ISSN 0001

Acta Obstetricia et Gynecologica Scandinavica

ol 58 1979 No 1

olished by
E NORDIC ASSOCIATION FOR OBSTETRICS AND GYNECOLOGY

Acta Obstetricia et Gynecologica Scandinavica

Official Publication of the Nordic Association for Obstetrics and Gynecology

Acta Obstetricia et Gynecologica Scandinavica publishes original papers and review articles on clinical and experimental research work in the fields of obstetrics and gynecology including perinatology gynecologic oncology and female urology It brings you up to date information on recent progress and international developments in these fields

All articles are published in English

Denmark Finland Iceland Norway and Sweden are represented on the Editorial Board

Specialists within various fields of obstetrics gynecology have made themselves availa referees

ta Obstetricia et Gynecologica Scandinavica is published 6 times annually each issue containing a minimum of 96 pages

Six issues constitute one volume

Price per volume Sw Crs 240 incl postage

Swedish subscribers Add V A T

Supplements will be delivered to subscribers free of charge

Editor

Professor Ingemar Joelsson
Department of Obstetrics and Gynecolog
Umeå University Hospital
S 901 85 Umeå Sweden

Administrative Editor

Miss Marie Charlotte Ivarsson Umeå

Editorial Office

Box 443
S 901 09 Umeå Sweden

Subscription and Distribution

Acta Obstetricia et Gynecologica Scandi
Box 443
S 901 09 Umeå Sweden
Postal giro account 45 09 22 0
Bank giro account 615 - 7531
Bank Skandinaviska Enskilda Banken
Account no 5329 20 039 54
Box 177 S 901 03 Umeå Sweden

Printing and Binding

Almqvist & Wiksell Tryckeri AB
S 751 81 Uppsala Sweden

Contents

Editorial 1

Grennert, L Persson P H Gennser G and *Kullander S* On improved outcome of twin pregnancies 3

Koller O Sagen N Ulstein M and *Vaula D* Fetal growth retardation associated with inadequate haemodilution in otherwise uncomplicated pregnancy 9

Little R E and *Hook E B* Maternal alcohol and tobacco consumption and their association with nausea and vomiting during pregnancy 15

Bille Brahe N E and *Rørth M* Red cell 2 3-diphosphoglycerate in pregnancy 19

Gordon Wright A P Dutt T P and *Elder M G* The routine use of oral prostaglandin E_2 tablets for induction or augmentation of labour 23

Arocha Pinango C L Linares J Cova A and *Martínez P* Is there a physiological intravascular coagulation in obstetrical cases? 27

Paterson M E L The aetiology and outcome of abruptio placentae 31

Naeye R L Tafari N and *Marboe C C* Perinatal death due to abruptio placentae in an African city 37

Nesheim B I Lindbæk E Storm Mathisen I and *Jenssen H* Neurobehavioral response of infants after paracervical block during labour 41

Beazley J M and *Swinhoe J R* Body weight in parous women Is there any alteration between successive pregnancies? 45

Feingold M Levin S and *Insler V* The peroxidase content and the antibacterial activity of the amniotic fluid 49

Guzmán V Toscano G Canales E S and *Zárate A* Improvement of defective lactation by using oral metoclopramide 53

O Herlihy C Early successful pregnancy following tuberculous endometritis 57

Nakano R Hashiba N Washio M and *Tojo S* Diagnostic evaluation of progesterone 59

Huggins G R Rosenfeld D L Rickels K Garcia C R and *Fischer E L* Emotional distress in morning after pill patients 65

Philpson A Plasma and urine levels produced by an oral dose of ampicillin 0 5 g administered to women taking oral contraceptives 69

Karam K and *Hajj S* Hyperthecosis syndrome 73

Magno R Medegård A Bengtsson R and *Tronstad S E* Acid base balance during laparoscopy 81

Cullberg G and *Larsson B* Some adverse effects of copper IUD 87

Öbrink A Fedor Freybergh P Hjelmkvist M and *Bunne G* Mental factors influencing recurrence of stress incontinence 91

Laatikainen T Nieminen U and *Adlercreutz H* Plasma medroxyprogesterone acetate levels following intramuscular or oral administration in patients with endometrial adenocarcinoma 95

Punnonen R Gronroos M and *Vaajalahti P* Squamous cell carcinoma in situ from the uterine cervix to the distal end of the fallopian tube 101

Reading A E Reed C and *Newton J R* A card sort method for pain assessment in gynaecology A multidimensional approach 105

Ulmsten U and *Andersson K E* Multichannel intrauterine pressure recording by means of microtransducers 115

Short communication

Ölund A The effect of indomethacin on the instillation abortion interval in rivanol induced mid trimester abortion 121

Letters to the editor

Öbrink A Bunne G Collen J and *Tjernberg B* Estrogen regimen in women with endometrial carcinoma at Radiumhemmet 1974-77 123

Serup J Vaginal fine-needle and large needle aspiration biopsy in large pelvic tumors indicating advanced ovarian carcinoma A new technique 125

Announcements

Int Symp on *Endocrine Pathology of the Ovary* 86
Xth World Congress on *Fertility and Sterility* 90
Postgraduate Course in *Reproductive Endocrinology* 90
Int Symp on *Human Placenta Proteins and Hormones* 100
Int Symp on *Adrenal Androgens* 100
List of National and International Congresses 1979 127
IXth World Congress of *Gynecology and Obstetrics* 128

Book reviews

Book reviews 114

Appended

Suppl 79 Regional changes in structure and function of adrenergic nerves in guinea pig uterus during pregnancy By Gunnar Thorbert

Suppl 80 Fetal movement monitoring in normal and high-risk pregnancy By Christman Ehrstrom

Acta Obstetricia et Gynecologica Scandinavica

Official Publication of the Nordic Association for Obstetrics and Gynecology

Acta Obstetricia et Gynecologica Scandinavica publishes original papers and review articles on clinical and experimental research work in the fields of obstetrics and gynecology including perinatology gynecologic oncology and female urology It brings you up to date information on recent progress and international developments in these fields

All articles are published in English

Denmark Finland Iceland Norway and Sweden are represented on the Editorial Board

Specialists within various fields of obstetrics and gynecology have made themselves available as referees

Acta Obstetricia et Gynecologica Scandinavica published 6 times annually each issue con[illegible] a minimum of 96 pages

[illegible] issues constitute one volume

Price per volume Sw Crs 240 incl postage

Swedish subscribers Add V A T

Supplements will be delivered to subscribers free of charge

Editor

Professor Ingemar Joelsson
Department of Obstetrics and Gynecology
Umeå University Hospital
S 901 85 Umeå Sweden

Administrative Editor

Miss Marie Charlotte Ivarsson Umeå

Editorial Office

Box 443
S 901 09 Umeå Sweden

Subscription and Distribution

Acta Obstetricia et Gynecologica Scandinavica
Box 443
S 901 09 Umeå Sweden
Postal giro account 45 09 22 0
Bank giro account 615 7531
Bank Skandinaviska Enskilda Banken
Account no 5329 20 039 54
Box 177 S 901 03 Umeå Sweden

Printing and Binding

Almqvist & Wiksell Tryckeri AB
S 751 81 Uppsala Sweden

Contents

Bergsjo P Bakketeig L and *Eikhom S N* Duration of labour with spontaneous onset 129

Jouppila R Jouppila P Karinen J M and *Hollmén A* Segmental epidural analgesia in labour related to the progress of labour fetal malposition and instrumental delivery 135

Fu Wang C and *Gemzell C* Pregnancy following treatment with human gonadotropins in primary unexplained infertility 141

Obel E Pregnancy complications following legally induced abortion with special reference to abortion technique 147

Kurjak A and *Latin V* Ultrasound diagnosis of fetal abnormalities in multiple pregnancy 153

Lauslahti K and *Ikonen S* Placenta as an indicator of fetal postnatal prognosis 163

Mandelin M and *Karjalainen O* Menstrual regulation as a method for early termination of pregnancy 169

Jaschevatzky O E Anderman S Shalit A Kampf D and *Grunstein S* The treatment of postmenopausal syndrome by monthly oral doses of Quinestrol 175

Carlstrom K Damber M G Furuhjelm M Joelsson I Lunell N O and *von Schoultz B* Serum levels of total dehydroepiandrosterone and total estrone in postmenopausal women with special regard to carcinoma of the uterine corpus 179

Bremme K and *Einhorn N* Prophylactic salpingo-oophorectomy in cancer of the cervix 183

Grönroos M Liukko P Rauramo L and *Punnonen R* Treatment of vulval epithelial lesions by pulsed high frequency therapy 187

Skjaeraasen J Amniotic fluid phospholipid concentration in pregnancy with preeclampsia and/or intrauterine growth retardation of the fetus 191

Maršál K Lofgren O and *Gennser G* Fetal breathing movements and maternal exercise 197

Brohult S Brohult A Brohult J and *Joelsson I* Effect of alcoxyglycerols on the frequency of fistulas following radiation therapy for carcinoma of the uterine cervix 203

Short communitations

Fianu S and *Vaclavincova V* External cephalic version in the management of breech presentation with special reference to placenta location 209

Backstrom T von Schoultz B and *Toivonen J* Plasma progesterone concentrations after administration via intravaginal rings 211

Johansson R Grönroos M Kuovonen I and *Lovgren T* Oestrogen receptors in dysplastic and malignant vulval tissue 213

Case Reports

Ingerslev M Failure of fusion between an upper and a lower segment of the vagina 215

Weinraub Z Langer R Bukovsky I Schneider D and *Caspi E* Ultrasonographic diagnosis of fetal ascites in a twin pregnancy 217

van Meir J M Drogendijk A C Wladimiroff J W and *Vielenga G* Colposcopy in a case of suspected genital herpes infection in early pregnancy 221

Appended

Suppl 81 Investigation of prostaglandins for abortion By Niels H Lauersen

Suppl 82. The regulation of oestradiol and progesterone concentrations in the female reproductive tissues By Satish Batra

Suppl 83 Epidural analgesia Continuous mini infusion of bupivacaine into the epidural space during labor By Alena Matouskova

Suppl 84 Cervical ripening induced by Prostaglandin E_2 in viscous gel By Ulf Ulmsten and Lars Wingerup

Suppl 85 Pharmacodynamic studies with a new progestational substance — org 2969 — in combination with ethinyloestradiol By U Alapiessa *et al*

Acta Obstetricia et Gynecologica Scandinavica

Submission of papers

Papers should be submitted as the top copy and one carbon or photostatic copy of the typewritten manuscript

Danish Finnish Icelandic and Norwegian contributors should send their manuscripts to the regional editor

Professor Dyre Trolle Gynekologisk-obstetrisk afd Y Rigshospi alet DK 2100 København N Denmark

• Professor Lauri Rauramo Kvinnokliniken Universi tetets Centralsjukhus SF 20520 Åbo 52 Finland

Dr Med Gunnlaugur Snædal Department of Obstetrics and Gynecology Landspitalinn Reykjavik Iceland

Dr Med Per Bergsjo Sentralsykehuset I Akershus N 1474 Nordbyhagen Norway

Contributions by Swed sh and non Nord'c authors should be addressed to the editor in Sweden

Submission of a manuscript is held to imply that the paper has not been published elsewhere and that if accepted it will not be republished in any other journal in the same or similar form without the Editor s consent

Language

Papers will be published in English It is essential that the language is irreproachable The cost of translation or linguistic revision shall be borne by the author The editors reserve the right to make any editorial changes they deem necessary

Arrangement

Manuscripts have to be in their final form when submitted They should be typewritten with double spacing and a wide left hand margin The *first page* should contain Title of paper a running headline author s name department *institution or hospital location and country The main title* ld contain words necessary for correct indexing and be as clarity permits

I *second page* should contain an abstract not exceeding 200 words and conta ning pertinent information on the material and methods used important results and major conclusions

The *third page* should begin with the *Introduction* part of the paper The subject matter should then be clearly ar*ranged with suitable head'ngs and subheadings The fol*lowing head ngs are preferred in this order *Material Methods Results Discussion Acknowledgements* and *References* Tables should be typed on separate sheets Each table must be accompanied by a descriptive title typed above the table to which it refers A suitable legend must be provided for each figure

Numerals should be used for weights measures percentages and degrees of temperature Weights and measures should be abbreviated accord ng to the International System of Units

Supplements

Authors are invited to publish manuscripts as supplements to Acta Obstetricia et Gynecolog ca Scand navica The cost of printing and b nd ng a supplement should always be defrayed by the author

Illustrations

Original illustrations should be submitted in the form of unmounted original artwork suitable for direct reproduction, Line drawings may also be submitted as reproductions on graphic material Half tone pictures should be submitted as glossy prints The figure number author s name and tit e of paper should appear on the back of every illustration Write this information lightly in soft pencil being careful not to break the emulsion on the photograph

The author should make sure that numerical and alphabetical notations within illustrations are large enough to be fully readable after size reduction

Figures and tables mentioned in the text should be referred to as Fig 1 and 'Table VII etc The approxima e position of figures and tables should be ind'cated in the margin

References

The reference list should contain only necessary references It shall be arranged alphabetically each reference being numbered Abbreviations should be in conformity with the style of *Index Medicus (New Series)* In this system abbreviation periods are omitted Examples

1 Cruickshank B & Stuart Smith D.A Orchitis associated with spermagglutinating antibod es Lancet *1* 708 1959

2 Fjällbrant B Immunoagglutination of sperm in cases of sterility Acta Obstet Gynecol Scand *44* 474 1965

3 Mann T The biochemistry of semen and of the male reproductive tract Methuen London 1964

4 Snyder F F & Hoskins F M *In* A textbook of Obstetrics (ed D E Reid) p 81 Saunders Philadelphia and London 1962

Italics are marked in the manuscript by underlining

When several papers by the same author are quoted the papers should be numbered in chronological order

Text references should be ind cated by figures within parentheses

General

Authors are requested in the interest of all concerned to restrict the length of papers — papers should not exceed 12 printed pages includ ng tables and illustrations If a paper exceeds 8 printed pages (about 20 typewritten sheets) the cost of typesetting and printing the excess pages will be borne by the author The cost of illustra ions printed in color as well as the cost of black and white illustrations in excess of Sw Crs 200 will be borne by the author The same applies to the cost of add tions or corrections requested by the *author after his manuscript has been typeset*

Proof prints and reprints

The printers proof will be sent to the pr ncipal author together with an order form for reprints The proof should be corrected and returned without delay

Contents

Skjaeraasen J and *Stray Pedersen S* Amniotic fluid phosphatidylinositol and phosphatidylglycerol 225

Lundstrom V Bremme K Eneroth P Nygård I and *Sundvall M* Serum beta-human chorionic gonadotrophin levels in the early diagnosis of ectopic pregnancy 231

Maltau J M Stokke K T and *Moe N* Effects of betamethasone on plasma levels of estriol cortisol and HCS in late pregnancy 235

Thaler I Zinder O Abramovici H and *Brandes J M* Serum and amniotic fluid heat labile alkaline phosphatase and aminotransferases in association with meconium stained liquor 239

Kulseng Hanssen S Torjesen P A and *Hanssen K F* Serum prolactin and thyroid stimulating hormone levels following thyreotropin releasing hormone stimulation in preeclamptic patients 245

Jouppila P Kuikka J Jouppila R and *Hollmén A* Effect of induction of general anesthesia for cesarean section on intervillous blood flow 249

Aarnoudse J G and *Huisjes H J* Complications of cerclage 255

Weber T and *Obel E* Pregnancy complications following conization of the uterine cervix (I) 259

Johansen P Arffmann and *Pallesen G* Evaluation of smears obtained by cervical scraping and an endocervical swab in the diagnosis of neoplastic disease of the uterine cervix 265

Henriksen H M The cryosurgical treatment of intraepithelial neoplasia 271

Liukko P Grönroos M Punnonen R and *Kilkku P* Methods for evaluating the intrauterine location of carcinoma 275

Ylostalo P Rantakyla P Jarvinen P A and *Kauppila E* Intrauterine progesterone contraceptive system as an alternative in cases where conventional IUD s are unsuitable 279

Honoré L Menorrhagia diffuse myometrial hypertrophy and the intrauterine contraceptive device 283

Allgén L G Holmberg G Persson B and *Sorbo B* Biological fate of methenamine in man 287

Fianu S and *Joelsson I* Minimal brain dysfunction in children born in breech presentation 295

Paavonen J A Saikku P Vesterinen E and *Lehtovirta P* Infertility and cervical chlamydia trachomatis infections 301

Case Reports

Sagen N Ulstein M Romslo I and *Støa K F* Plasma estriol progesterone cortisol placental lactogen and alpha fetoprotein in a pregnancy with an anencephalic fetus followed from the seventh week till term 305

Nielsen J Kristoffersen E and *Homma A* X/X translocation and Turner's syndrome in a woman with climacterium praecox 309

Sadovsky E Laufer N and *Beyth, Y* The role of fetal movements assessment in cases of severe Rh immunized patients 313

Lindberg B S Maternal sepsis uterine rupture and coagulopathy complicating cervical cerclage 317

Appended

Suppl 86 Risk factors in endometrial carcinoma with special reference to the use of estrogens By Tuula Salmi

Suppl 87 Dysmenorrhea and prostaglandins Editors N Wiqvist O Widholm S J Nillius and B Nilsson.

Suppl 88 New leads on hormonal contraception and hormone therapy of the climacteric and menopause Editor G Zador

Suppl 89 Hemodynamic investigations during labour and delivery By K Kjeldsen

Suppl 90 Electromyographic observations on the human uterus during labour By G M J A. Wolfs and M van Leeuwen.

Acta Obstetricia et Gynecologica Scandinavica

Submission of papers

Papers should be submitted as the top copy and one carbon or photostatic copy of the typewritten manuscript

Danish Finnish Icelandic and Norwegian contributors should send their manuscripts to the regional editor

- Professor Dyre Trolle Gynekologisk-obstetrisk afd Y Rigshospitalet DK 2100 København N Denmark
- Professor Lauri Rauramo Kvinnokliniken Universitetets Centralsjukhus SF 20520 Åbo 52 Finland
  Dr Med Gunnlaugur Snaedal Department of Obstetrics and Gynecology Landspitalinn Reykjavik Iceland
- Dr Med Per Bergsjø Sentralsykehuset i Akershus N 1474 Nordbyhagen Norway

Contributions by Swedish and non Nordic authors should be addressed to the editor in Sweden

Submission of a manuscript is held to imply that the paper has not been published elsewhere and that if accepted it will not be republished in any other journal in the same or similar form without the Editor s consent

Language

Papers will be published in English It is essential that the language is irreproachable The cost of translation or linguistic revision shall be borne by the author The editors reserve the right to make any editorial changes they deem necessary

Arrangement

Manuscripts have to be in their final form when submitted They should be typewritten with double spacing and a left hand margin The *first page* should contain Title paper a running headline author s name department tution or hospital location and country The main title should contain words necessary for correct indexing and be as brief as clarity permits

The *second page* should contain an abstract not exceeding 200 words and containing pertinent information on the material and methods used important results and major conclusions

The *third page* should begin with the *Introduction* part of the paper The subject matter should then be clearly arranged with suitable headings and subheadings The following headings are preferred in this order *Material Methods Results Discussion Acknowledgements* and *References* Tables should be typed on separate sheets Each table must be accompanied by a descriptive title typed above the table to which it refers A suitable legend must be provided for each figure

Numerals should be used for weights measures percentages and degrees of temperature Weights and measures should be abbreviated according to the International System of Units

Supplements

Authors are invited to publish manuscripts as supplements to Acta Obstetricia et Gynecologica Scandinavica The cost of printing and binding a supplement should always be defrayed by the author

Illustrations

Original illustrations should be submitted in the form of unmounted original artwork suitable for direct reproduction Line drawings may also be submitted as reproductions on graphic material Half tone pictures should be submitted as glossy prints The figure number author s name and title of paper should appear on the back of every illustration Write this information lightly in soft pencil being careful not to break the emulsion on the photograph

The author should make sure that numerical and alphabetical notations within illustrations are large enough to be fully readable after size reduction

Figures and tables mentioned in the text should be referred to as Fig 1 and Table VII etc The approximate position of figures and tables should be indicated in the margin

References

The reference list should contain only necessary references It shall be arranged alphabetically each reference being numbered Abbreviations should be in conformity with the style of *Index Medicus (New Series)* In this system abbreviation periods are omitted Examples

1. Cruickshank B & Stuart Smith D A Orchitis associated with spermagglutinating antibodies Lancet *1* 708 1959
2. Fjällbrant B Immunoagglutination of sperm in cases of sterility *Acta Obstet Gynecol Scand* *44* 474 1965
3. Mann T The biochemistry of semen and of the male reproductive tract Methuen London 1964
4. Snyder F F & Hoskins F M *In* A textbook of Obstetrics (ed D E Reid) p 81 Saunders Philadelphia and London 1962.

Italics are marked in the manuscript by underlining

When several papers by the same author are quoted the papers should be numbered in chronological order

Text references should be indicated by figures within parentheses

General

Authors are requested in the interest of all concerned to restrict the length of papers — papers should not exceed 12 printed pages including tables and illustrations If a paper exceeds 8 printed pages (about 20 typewritten sheets) the cost of typesetting and printing the excess pages will be borne by the author The cost of illustrations printed in color as well as the cost of black and white illustrations in excess of Sw Crs 200 will be borne by the author The same applies to the cost of additions or corrections requested by the author after his manuscript has been typeset

Proof prints and reprints

The printers proof will be sent to the principal author together with an order form for reprints The proof should be corrected and returned without delay

Contents

Lykkesfeldt G and *Osler M* A comparison of three methods for inducing labor: Oral prostaglandin E_2 buccal desaminooxytocin intravenous oxytocin 321

Vugt van P J H The protrusions from the cervical canal at the scar of a previous cesarean section 327

Maršál K Gennser G and *Lofgren O* Effects on fetal breathing movements of maternal challenges Cross-over study on dynamic work static work passive movements hyperventilation and hyperoxygenation 335

Rolschau J Date J and *Kristoffersen K* Folic acid supplement and intrauterine growth 343

Weber T and *Obel E B* Pregnancy complications following conization of the uterine cervix (II) 347

Bergstrom S Amniotic fluid cell exfoliation in early human pregnancy 353

Briel R C Kunz S and *Kidess E* Platelet function coagulation and fibrinolysis during termination of missed abortion and missed labor by $PGF_{2\alpha}$ and oxytocin 361

Hertz J B Falck Larsen J Svenstrup B and *Johnsen S G* Estradiol estriol and human placental lactogen in serum in threatened abortion 365

Levin S Amsterdam E Brook I and *Insler V* The effect of missed abortion and spontaneous abortion on the fate of subsequent pregnancies 371

Kullander S and *Svanberg L* Bromocriptine treatment of the premenstrual syndrome 375

Andersen A N Larsen J F Eskildsen P C Knoth M Micic S Svenstrup B and *Nielsen J* Treatment of hyperprolactinemic luteal insufficiency with bromocriptine 379

Nyholm H and *Plesner R* Serum testosterone FSH/LH and urine excretion of estrogens and corticoids during treatment with an injectable longacting estrogen DHEA preparation 385

Punnonen R Kouvonen I Lovgren T and *Rauramo L* Uterine and ovarian estrogen receptor levels in climacteric women 389

Cittadini A Castaldo F Paparella P Romor R Carelli G Bompiani A and *Terranova T* Water and ion metabolism in placenta II Water compartment and electrolytes in slices of rabbit placenta at different periods of gestation incubated at 0 – 1 C 393

Onsrud M Gjønnæss H and *Bergan T* Amoxycillin absorption and penetration in pelvic inflammatory disease 401

Johnsson J E Recurrences and metastases in carcinoma of the uterine body correlated to the size and localization of the primary tumor 405

Short communications

Gustavii B Cordesius E Lofberg L and *Stromberg P* Fetoscopy 409

Halbrecht I Komlos L and *Ben-Efraim S* Mixed wife-husband leukocyte migration inhibition test after normal pregnancy 411

Ishiguro T and *Ozaki Y* Neutralizing antibodies against herpes simplex virus in maternal and umbilical cord serum 413

Case Report

Goldman J A Peleg D Agmon M and *Shapiro G* Arteriography and chemotherapy in localized trophoblastic disease by means of local (pelvic) intraarterial infusion 415

Acta Obstetricia et Gynecologica Scandinavica

Submission of papers

Papers should be submitted as the top copy and one carbon or photostatic copy of the typewritten manuscript

Danish Finnish Icelandic and Norwegian contributors should send their manuscripts to the regional editor

- Professor Dyre Trolle Gynekologisk-obstetrisk afd Y Rigshospitalet DK 2100 København N Denmark
- Professor Lauri Rauramo Kvinnokliniken Universitetets Centralsjukhus SF 20520 Åbo 52, Finland
- Dr Med Gunnlaugur Snædal Department of Obstetrics and Gynecology Landspitalinn Reykjavik Iceland
- Dr Med Per Bergsjø Sentralsykehuset i Akershus N 1474 Nordbyhagen Norway

Contributions by Swedish and non Nordic authors should be addressed to the editor in Sweden

Submission of a manuscript is held to imply that the paper has not been published elsewhere and that if accepted it will not be republished in any other journal in the same or similar form without the Editor s consent

Language

Papers will be published in English It is essential that the language is irreproachable The cost of translation or linguistic revision shall be borne by the author The editors reserve the right to make any editorial changes they deem necessary

Arrangement

have to be in their final form when submitted should be typewritten with double spacing and a left hand margin The *first page* should contain Title of paper a running headline author s name department institution or hospital location and country The main title should contain words necessary for correct indexing and be as brief as clarity permits

The *second page* should contain an abstract not exceeding 200 words and containing pertinent information on the material and methods used important results and major conclusions

The *third page* should begin with the *Introduction* part of the paper The subject matter should then be clearly arranged with suitable headings and subheadings The following headings are preferred in this order *Material Methods Results Discussion Acknowledgements* and *References* Tables should be typed on separate sheets Each table must be accompanied by a descriptive title typed above the table to which it refers A suitable legend must be provided for each figure

Numerals should be used for weights measures percentages and degrees of temperature Weights and measures should be abbreviated according to the International System of Units

Supplements

Authors are invited to publish manuscripts as supplements to Acta Obstetricia et Gynecologica Scandinavica The cost of printing and binding a supplement should always be defrayed by the author

Illustrations

Original illustrations should be submitted in the form of unmounted original artwork suitable for direct reproduction. Line drawings may also be submitted as reproductions on graphic material Half tone pictures should be submitted as glossy prints The figure number author s name and title of paper should appear on the back of every illustration Write this information lightly in soft pencil being careful not to break the emulsion on the photograph

The author should make sure that numerical and alphabetical notations within illustrations are large enough to be fully readable after size reduction

Figures and tables mentioned in the text should be referred to as Fig 1" and "Table VII etc The approximate position of figures and tables should be indicated in the margin

References

The reference list should contain only necessary references It shall be arranged alphabetically each reference being numbered Abbreviations should be in conformity with the style of *Index Medicus (New Series)* In this system abbreviation periods are omitted Examples

1 Cruickshank B & Stuart Smith D A Orchitis associated with spermagglutinating antibodies Lancet *1* 708 1959
2. Fjällbrant B Immunoagglutination of sperm in cases of sterility Acta Obstet Gynecol Scand *44* 474 1965
3 Mann T The biochemistry of semen and of the male reproductive tract Methuen London 1964
4 Snyder F F & Hoskins F M *In* A textbook of Obstetrics (ed D E Reid) p 81 Saunders Philadelphia and London 1962

Italics are marked in the manuscript by underlining

When several papers by the same author are quoted the papers should be numbered in chronological order

Text references should be indicated by figures within parentheses

General

Authors are requested in the interest of all concerned to restrict the length of papers — papers should not exceed 12 *printed pages* including tables and illustrations If a paper exceeds 8 printed pages (about 20 typewritten sheets) the cost of typesetting and printing the excess pages will be borne by the author The cost of illustrations printed in color as well as the cost of black and white illustrations in excess of Sw Crs 200 will be borne by the author The same applies to the cost of additions or corrections requested by the author after his manuscript has been typeset

Proof prints and reprints

The printers proof will be sent to the principal author together with an order form for reprints The proof should be corrected and returned without delay

Contents

Hammarstrom L Fuchs T and *Smith C I E* The immunodepressive effect of human glucoproteins and their possible role in the nonrejection process during pregnancy 417
Ottesen B and *Lebech P E* Plasma progesterone serum estriol and plasma HPL determinations during the last trimester to detect changes before spontaneous labor 423
Gal D Choudry R Ung K A Abadir A and *Tancer L* Segmental epidural analgesia for labor and delivery 429
Skjæraasen J and *Stray Pedersen S* Amniotic fluid phosphatidylinositol and phosphatidylglycerol II Diabetic and preeclamptic pregnancies 433
Varma K Heine M W Haller W S Row A D Railsback, K and *Varma S K* Ratio of amniotic fluid cortisol and maternal serum cortisol (AFC/MSC) as an index of fetal lung maturity 439
Lunell N O Persson B Aragon G Fredholm B B and *Åström H* Circulatory and metabolic effects of acute $beta_1$-blockade in severe pre-eclampsia 443
Lammintausta R and *Erkkola R* Effect of long term salbutamol treatment on renin-aldosterone system in twin pregnancy 447
Ylikorkala O Kauppila A and *Ollanketo M L* Intramuscular ACTH or placebo in the treatment of hyperemesis gravidarum 453
Hasch E Lange A. P and *Sørensen T* Prediction of the time of delivery by means of ultrasonic scanning between the 20th and 30th weeks of pregnancy 457
Jouppila P Vaginal bleeding in the last two trimesters of pregnancy A clinical and ultrasonic study 461
De Gezelle H Dhont, M Thiery M and *Parewyck, W* Puerperal lactation suppression and prolactin 469
Bergqvist A Bergqvist, D and Hallbook T Acute deep vein thrombosis (DVT) after cesarean section 473
Gronroos M Liukko P Kilkku and *Punnonen R* Pregnancy and delivery after conization of the cervix 477
Møller B R Mommsen S Bøggild Madsen N B Vestersgaard Andersen T B Olcott, A and *Tner Hansen T* Effect of althesin anesthesia on blood loss during therapeutic abortion A comparison with local and thiopental anesthesia 481
Obel E B Pregnancy complications following legally induced abortion 485
Dalaker K Moe Lichtenberg S and *Økland G* Delayed reproductive complications after induced abortion 491

Short communication

Nielsen N C Hansen R and *Larsen T* Heat inducation in copper bearing IUD s during short-wave diathermy 495

Case Reports

Bryson T K Benumof J L and *Fanna J R* Uterine rupture caused by midtrimester saline abortion 497
Kirschner R Löfstrand T and *Mark, J* Pregnancy in a non-communicating rudimentary uterine horn A reason for failed therapeutic second trimester abortion 499
De Grandi P Janecek, P and *Lambercy J M* Abscess formation of a Gartner's duct cyst with cervical communication in a case of bicornuate uterus associated with an ipsilateral renal agenesis 503
Gupta S Gupta I M and *Tiwari P V* In-situ carcinoma of the uterine cervix showing superficial endometrial spread 507

Letter to the editor *by E. Rubinstein*

509

Appended

Suppl 91 Hormonal factors in the regulation of myometrial activity An in vivo study By Tadeusz Laudański

ON IMPROVED OUTCOME OF TWIN PREGNANCIES

Per Håkan Persson Lars Grennert Gerhard Gennser and Stig Kullander

From the Department of Obstetrics and Gynecology
University of Lund Allmänna Sjukhuset S-214 01 Malmö Sweden

Abstract During the past four years an attempt has been made in Malmö to reduce the frequency of preterm termination of twin pregnancies For this purpose the entire pregnant population of this medium sized city was subjected to general ultrasonic screening in the second trimester This detected 88 per cent of the twin pregnancies The screening had a methodological error of 2 per cent Eightysix of the women with twin pregnancy were subjected to bedrest in hospital for more than two weeks in the second half of gestation The incidences of twins born with birth weight below 1 500 g and of twins light for gestational age were reduced compared with those a decade earlier Also the group of twins born before the 37th week decreased and the perinatal mortality rate fell to the same level as in singleton pregnancies Early detection of twin pregnancies followed by rest for the pregnant women seems to contribute to an improved outcome of these gestations

Neonatal mortality is affected by immaturity at birth (12 37 32) Measures to prevent preterm deliveries can be expected to reduce neonatal wastage Multiple pregnancies involve a particular risk for premature termination of gestation (1 20 23 28 30 34) and a high perinatal mortality (5 15 16 23 24 28 33 36) Among twins there is also a high percentage of infants with mental and neurological handicap inflicted at birth reflecting the general finding that the incidence of these damages is increased in infants after preterm delivery (3 4 8) It has been repeatedly demonstrated that the impaired development of the central nervous system in twins is due to factors associated with low birth weight and preterm delivery (22 25 31 40 41) An increase in the average gestational lenght of multiple pregnancies would therefore be expected to decrease the mortality of twin infants and reduce the chronic handicaps in the survivors

In the 1950 s Bender (7) suggested that bedrest could prevent inadvertent preterm delivery of twins but only some later clinical studies have supported this hypothesis (6 19 25 27) On the other hand an increased birth weight is reported to follow admission to hospital before term (2 10 21 22) Preventive treatment of twin pregnancies with bedrest has been widely attempted but its intended effects have not been proved unanimously for mainly two reasons Multiple gestations — even if detected before delivery — have often been diagnosed too late for preventive measures to achieve their optimum results Moreover before the introduction of a general twin screening the twins detected early in gestation and subjected to preventive treatment have presumably been the largest and most well nourished fetuses This has undoubtedly affected the interpretation of the results

An extensive and early diagnosis of gestational multiplicity is therefore of paramount importance for the evaluation of the effect of bedrest in reducing prematurity This initiated the application of various methods for large scale screening for multiple pregnancies e g improved history taking more alert physical examination (39) hormonal screening (17 18 29) and ultrasound (28 35) Of these methods large scale ultrasonic examination has so far proved superior (18)

The present paper summarizes a four year experience of ultrasonic screening as a prerequisite for an extensive early hospitalization of women with twin pregnancies It reports the outcome of these pregnancies concerning duration of gestation birth weight and perinatal mortality

PATIENTS AND METHODS

The study took place at the University Hospital of Malmö during 1 1 1973 30 4 1977 when 12 098 women were delivered During this period 110 pairs of twins were born an apparent frequency of 1 110 The maternity hospital reported in the study is the only one serving a city of 250 000 inhabitants and most of the population attend the antenatal clinics of the hospital Private obstetricians working in close collaboration with the hospital staff saw 20 per cent of the pregnant women Ninetyseven of the 110 twin pairs were detected early in gestation and 86 women accepted the preventive programme They comprise the study group (Group I) No conventional control group could be formed (see Discussion) but comparisons were made with the 24 women who were non acceptors or whose twin pregnancy was not

Table I *Birth weights*

	< 1500 g		1500-2500 g		> 2500 g		Total
Group	n	%	n	%	n	%	n
I	0	0	75	44	97	56	172
II	5	10	25	52	18	38	48
III	9	5	81	44	96	52	186

I/II p < 0 01 I/III p < 0 05

detected before delivery (Group II) Further comparison were also made with the 93 twin pairs born at the same maternity hospital during 1963 1965 when both early diagnosis and prevention of prematurity were lacking (Group III) During this period 11 733 deliveries occurred (apparent *twin frequency 1 122)*

All the pregnant women were referred to ultrasonic screening at their first attendance at the antenatal clinic The ultrasonic examinations were initially performed in the 28th week During the course of the investigation it was found desirable to perform the screening as early as practical This reduced the average gestational age for the ultrasonic screening to 19 weeks

Two obstetricians and especially trained midwives at the Ultrasonic Laboratory performed the examinations every operator doing in turn 25 screenings a day To avoid monotony the midwives did part time ultrasonic screening alternating with duties at the delivery ward This schedule a... fatigue and diagnostic failures Every examination ...scheduled to take 15 min and apart for the number of ...es the position of the fetus and the placenta and the ...ize of the fetal head were assessed Most examinations were performed with a Kretz Technik Combison II

After the diagnosis of multiple pregnancies the women were prescribed absence from work and rest at home They were seen at three weekly intervals at the clinics until the beginning of the 29th week when they were admitted into the maternity hospital During the subsequent hospitalization the prevention for preterm delivery consisted solely of rest no drugs for uterine relaxation being used even when uterine contractions occurred *The mean duration of hospitalization* was 55 days The women were supervised for the appearance of pre-eclamptic signs and their domestic and nursing problems were taken care of by social welfare officers If no further complications occurred the women were allowed home for weekends After the end of the 36th week they were discharged form the hospital provided that their pregnancy course had been completely normal Otherwise hospital care was extended until delivery Few multiple pregnancies were allowed to exceed the 38th week at which time inductions were performed by amniotomy and i v oxytocin administration In a few patients preventive hospitalization commenced later than the 5th week and was terminated (mostly for social reasons) before the 36th week No twin pregnancies lasting less than 8 gestational weeks are included in this report Triplets are excluded

To evaluate the benefit of improved history taking for diagnosis a detailed questionnaire *regarding the familiar incidence of multiplicity was answered by 5 272 of the pregnant* women before the ultrasonic examination under the guidance of a trained interviewer

In all women the gestational age was estimated from the last menstrual period by Naegele s calculation and from the early clinical assessment of uterine size The following statistical tests were used Student s t test Chi square test with Yates correction and exact permutation test with each pregnancy (and not the individual twin) as the independent variable of comparison All tests were one sided

RESULTS

During the study period ultrasound was used to screen an increasing part of the pregnant population When the programme was in full effect more than 90 per cent of the women participated Ninetyseven out *of the 110 twin pregnancies were detected in the programme* i e a discrimination rate of 88 per cent Two of the examined twin pregnancies (2 per cent) were mistakenly interpreted as singletons No falsely positive diagnosis of twins was made The net magni*tude of methodological error (2 per cent) agrees well* with our over all twin detection results as we have hitherto detected *145* out of *148* twin pairs by ultrasound

The average gestational age of twin pregnancies at the time of the detection was 35 weeks during 1963 1965 The mean gestational age for twin detection decreased from 30 weeks in 1973 to 20 weeks in 1977 The percentage of twin pregnancies discovered only after the birth of the first twin was 57 per cent in 1963 1965 and 2 per cent during 1973 1977

There was no increase in the average *birth weight* of the twins in the study group from 1973 1977 (Group I) compared with Groups II and III No consistent difference in birth weight between the first and *second born twins was noted Fortynine per cent* of twins born in 1973 1977 had a birth weight below 2 500 g the corresponding figure for 1963 1965 was 48 per cent No twins with very low birth weight (<1 500 g) appeared in the group with bedrest (Group I) Table I Also the percentage of twins that were light for gestational age (below the mean 2 SD of Swedish standard values for singletons [14]) was less in Group I (16 per cent) than in Groups II (27 per cent) and III (24 per cent) All twins born light for gestational age in Group I were born after the 35th week of gestation

The frequency of *pre-term deliveries* (before the 37th week) in Group I was 20 per cent and in Group II and III 33 per cent When only the twins born during the last 1½ years were considered during which period the programme was carried through most con

Table II *Mean gestational age of preterm delivered twins*

	Gestational age		
Group	Day	Week	n
I	240	34 6	17
II	233	33 5	8
III	235	33 8	31

Table III *Perinatal mortality*

	Ante partum		Post partum		Total	
Group	n	%	n	%	n	%
I	1	0 6	0	0	1	0 6
II	2	4 2	3	6 3	5	10 5
III	3	1 6	8	4 3	11	5 9

I/II p < 0 02 I/III < 0 02

sistently both concerning early detection of twins and the extent of hospitalization a significant decrease in pre term deliveries to 10 per cent was noted compared with the controls from 1963 1965 (p<0 01) The *pre term delivered* twins were born at a mean of 240 days in Group I 7 days later than in Group II (Table II) In Group I no twins were born before the 33rd week while in Group III 23 per cent of the pre term delivered twins were born before this week

In the group with bedrest *delivered at term* 85 per cent were induced (17 per cent cesarean section) in the 38th (range 37 40) week This is in contrast to the group from 1963 1965 where only 6 per cent (2 per cent cesarean section) were induced and the average delivery occurred in the 39th gestational week This difference in the management of the delivery invalidates comparison of birth dates between the groups of twins delivered after the 36th week

The *perinatal mortality* among the twins in the group with bedrest (0 6 per cent) was lower than in Groups II and III (p<0 02) Table III The perinatal mortality of twins in the present study group is of similar low magnitude to that of singleton pregnancies presently valid at our unit Only one fetus was lost among the 86 pairs of twins this occurred ante partum in the 37th week to a mother with severe sarcoidosis with degenerations in the walls of the maternal placental vessels The *deaths* among the twins in the groups of comparison in the *neonatal period* (Table III) were ascribed to lung immaturity except for one instance of cerebral hemorrhage During 1963 1965 23 per cent of the twin mothers had pre eclampsia in 1973 1977 the incidence was 10 per cent but the character of this complication was generally less severe

Evaluation of the questionnaires did not reveal any difference concerning the familiar incidence of twins between those who subsequently delivered twins and those who delivered singletons

DISCUSSION

In the present study the two control groups are not directly comparable to the study group in several respects As positive experience of bedrest for preventing premature expulsion of the twin fetuses has been reported (6 19 25 27) it was considered ethically impracticable to form a comparable group of women where after detection of twins preventive measures were purposely withheld Moreover it must be emphasized that knowledge of the twin diagnosis reduces the prerequisites for correct comparison between groups by influencing the attitude of the physician and the patient to the pregnancy To achieve a nonobjectionable control group the diagnosis would have to be hidden from both the doctor and the patient Thus it was impossible to select a control group in its strict sense

Of the two groups for comparison one (Group III) differs by ten years from the study group Whether a spontaneous improvement of the outcome of twin pregnancy (regardless of early detection and interventions) would have occurred during this time cannot be determined However during these ten years no general change in the incidence of preterm delivery or in the incidence of low birth weight infants has occurred in our unit (9 26) On the other hand the perinatal mortality decreased from 2 1 in 1964 to 1 1 in 1974 The comparison with the contemporary group (II) suffers from the facts that half of these patients refused preventive treatment after multiple pregnancy had been diagnosed and the other half was not diagnosed in ample time suggesting a difference towards the study group regarding social class and attitudes In spite of the inadequacies of the groups chosen for comparison the differences found between the groups do not seem to be overestimated as international data from the seventies (32) do not support the concept of a spontaneous improvement in the fate of twin pregnancies

The most evident feature noted in the study group

was the *reduction of perinatal mortality* from the level present in 1963–1965. The perinatal mortality rate among the twins had, with rest as the only intervention, reached the mortality level of singleton pregnancies. The effect of the treatment on *prolongation of pregnancy* was evident in two ways: an absolute reduction of all preterm deliveries and an almost complete abolition of the very early spontaneous termination of gestation (before the 33rd week). But the treatment did not increase the *average birth weight*. The paradoxical non appearance of an improvement in the mean birth weight is most readily explained by the more active attitude in obstetrics practiced in recent years, which terminates twin gestations before the 39th week. The study group also comprised a lower *frequency of births of twins born light for gestational age* according to Swedish standards for singletons (14). This improvement mainly affected the group born after the 35th week. Our finding agrees with the experience that the size of twins tends to be the same as that of singletons during the major part *of the gestation and that not until the last six weeks* does the growth rate of twins tend to decrease (13). The reduction in the number of light for-date [illegible] born near term can be interpreted as a quality [illegible] (11) exerted by the preventive measures in the twin fetuses at the end of gestation.

How to obtain twin diagnosis The existence of hereditary components among the causal factors for twinning is not definitely proved. The Weinberg (1909) material (38) showed a preponderance of dizygotic twins among women with earlier multiple gestation. We do not support the familiar factor; this might be due to the smallness of our groups. However, our interviews were not meant to settle the question of genetic influence, but to evaluate whether an interrogation on the familiar twinning incidence would provide a basis for the selection of a target group of gravid women at risk for multiple pregnancy. Our study reveals that no obvious benefit in this respect is obtained from such interviews.

In our experience, the mere increase of clinical observation during antenatal visits increased the rate of twin detection. However, this method was far from satisfactory (60 per cent of the twins were detected before delivery by this means); moreover, the diagnosis was obtained regrettably late.

The available biochemical screening methods for early twin diagnosis with hormonal substances such as HPL, HCG, proteins such as AFP, and enzymes such as CAP might offer a considerable advantage in communities with poor ultrasonic facilities. But these tests do not establish a diagnosis *per se*, as none of them are sufficiently specific. Consequently they should be used to select a target group for further diagnostic measures. Of these, ultrasound has proved to be superior (18), and has in most hands reached a diagnostic detection rat of 96–98 per cent (18, 35). To the best of our knowledge, the present paper is the first report on a large scale general screening of a pregnant population for twins with ultrasound, which seems at present to be the only available method that offers a safe, reliable and early twin detection.

When is the optimum time for preventive measures? The presented data suggest that the combination of *early and complete detection of twin gestation and* bedrest leads to a decrease of perinatal mortality, postponement of the date of delivery and a reduction of the number of twins in the lowest birth weight classes. The study allows no definite conclusion about the latest desirable time for the diagnosis and for *commencement of the pre term prevention*. Obviously, preventive measures must be initiated well before the period of greatest risk for pre term labor. It has been demonstrated earlier that the perinatal wastage of twins born in the last trimester of pregnancy increases with decreasing gestational length, but the absolute number of twins of very low birth weight is low (7), thus reducing the magnitude of the medical problem. Several investigators (6, 31, 26) have claimed the 29–30th week to be the optimum time for the onset of prevention, and the present results do not disagree with this opinion. The time for the onset of prevention must be a compromise between the desirable and the practical. An accurate diagnosis should be reached well before this stage, at least before the 28th seek. Additional benefits can be expected from very early twin detection, such as preparing the pregnant women psychologically for the special risks of the gestation and alerting the physician to early signs of pregnancy complications. This might be as important for the pregnancy outcome as the later bedrest period.

ACKNOWLEDGEMENTS

We thank Bo Gullberg, Department of Statistics, University of Lund, for valuable statistical advice. The conscientious technical assistance of Mrs. Carla Jacobsson is gratefully acknowledged.

REFERENCES

1 Aaron J B Halperin J Fetal survival in 376 twin deliveries Am J Obstet Gynecol 69 794 1955

2 Ahlström K Prematurprofylax vid tvillinggraviditet Läkartidningen 71 3089 1974

3 Alberman E In Fetal Physiology and Medicine Saunders London 1976

4 Allen G & Kallmann F J Frequency and types of mental retardation in twins Am J Hum Genet 7 15 1955

5 Barr A & Stevenson A C Stillbirths and infant mortality in twins Ann Hum Genet 25 131 1961

6 Barter R H Hsu I Erkenbeck R V & Pugsley L Q The prevention of prematurity in multiple pregnancy Am J Obstet Gynecol 91 787 1965

7 Bender S Twin pregnancy A review of 472 cases J Obstet Gynaecol Br Emp 59 510 1952

8 Bjerre I Neurological investigation of 5 year-old children with low birth weight Acta Paediatr Scand 64 859 1975

9 Bjerre I In Epidemiology and Prognosis in Low Birth weight M D Thesis Malmö 1975

10 Brown E J & Dixon H G Twin pregnancy J Obstet Gynaecol Br Comm 70 251 1963

11 Butler N R & Bonham D G In Perinatal Mortality The First Report of the 1958 British Perinatal Mortality Survey Livingstone Edinburgh 1963

12 Clifford S H High risk pregnancy I Prevention of prematurity the sine qua non for reduction in mental retardation and other neurologic disorders New Eng J Med 271 243 1964

13 Daw E & Walker J Biological aspects of twin pregnancy in Dundee Br J Obstet Gynaecol 82 29 1975

14 Engström L & Sterky G Standard kurovor för vikt och längd hos nyfödda barn Läkartidningen 63 4922 1966

15 Farooqui M O Grossman III J H & Shannon R A A review of twin pregnancy and perinatal mortality Obstet Gynecol Surv 28 144 1973

16 Ferguson W F Perinatal mortality in multiple gestations Obstet Gynecol 23 861 1964

17 Gaspard U & Franchimont P HCS HCG and HCG subunits serum levels during multiple pregnancies Acta Genet Med Gemellol Suppl 22 195 1974

18 Grennert L Persson P H Gennser G & Kullander S Ultrasound and HPL screening for early detection of twin pregnancy Lancet i 4 1976

19 Guttmacher A F & Kohl S G The fetus of multiple gestations Obstet and Gynecol 12 528 1958

20 Ho SK & Wu PYK Perinatal factors and neonatal morbidity in twin pregnancy Am J Obstet Gynecol 122 979 1975

21 Jeffrey R L Bowes Jr W A & Delaney J J Role of bed rest in twin gestation Obstet and Gynecol 43 8 ? 1974

2 Jonas E G The value of prenatal bedrest in multiple pregnancy J Obstet Gynaecol Br Comm 70 461 1963

23 Jouppila P Kauppila A Koivisto M Moilanen I & Ylikorkala O Twin pregnancy The role of active management during pregnancy and delivery Acta Obstet Gynecol S and Suppl 44 13 1975

24 Kidess E & Heidecker K Gefährdung der Zwillingsschwangerschaft Med Welt 25 2144 1974

25 Koivisto M Jouppila P Kauppila A Moilanen J & Ylikorkala O Twin pregnancy Neonatal morbidity and mortality Acta Obstet Gynecol Scand Suppl 44 21 1975

26 Kullander S Unpublished observation

27 Laursen B Twin pregnancy Acta Obstet Gynecol Scand 52 367 1973

28 Minogue M A review of twin pregnancies National Maternity Hospital (1967 1971) J Ir Med Ass 67 181 1974

29 Mägiste M v Schenck H Sjöberg N O Thorell J I & Åberg A Screening for detecting twin pregnancy Am J Obstet Gynecol 126 697 1976

30 Powers W F Twin pregnancy Complications and treatment Obstet Gynecol 42 795 1973

31 Robertson J G Twin pregnancy Influence of early admission on fetal survival Obstet Gynecol 23 854 1964

32 Rush R W Keirse M J N C Howat P Baum J D Andersson A B M & Turnbull A C Contribution of preterm delivery to perinatal mortality Br Med J 2 965 1976

33 Russell J K Maternal and foetal hazards associated with twin pregnancy J Obstet Gynaecol Br Emp 59 208 1952

34 Skalba H Osuch Jaczewska R Lempart O & Ocharska Z Multiple pregnancy complications Acta Genet Med Gemellol Suppl 22 22 1974

35 Sunden B Ultrasound in the diagnosis of twins and hydramnios J Obstet Gynaecol Br Comm 72 952 1965

36 Tow S H Foetal wastage in twin pregnancy J Obstet Gynaecol Br Comm 66 444 1959

37 Usher R H & MacLean F H In Scientific foundations of pediatrics Heineman London 1974

38 Weinberg W Die Anlage zur Mehrlingsgeburt beim Meuschen und Ihre Vererbung Arch Rassenbio 6 322 1909

39 Westin B Scientific exhibition of the Fifth European Congress of Perinatal Medicine Uppsala Sweden 1976

40 Willerman L & Churchill J A Intelligence and birth weight in identical twins Child Dev 38 623 1967

41 Yue S J Multiple births in cerebral palsy Am J Phys Med 34 335 1955

Submitted for publication October 3 1977

Lars Grennert M D
Department of Obstetrics and Gynecology
University of Lund
Allmänna sjukhuset
S-214 01 Malmö
Sweden

Acta Obstet Gynecol Scand 58 9–13 1979

FETAL GROWTH RETARDATION ASSOCIATED WITH INADEQUATE HAEMODILUTION IN OTHERWISE UNCOMPLICATED PREGNANCY

O Koller N Sagen M Ulstein and D Vaula

From the Department of Obstetrics and Gynecology and the EDB section of the Medical Faculty of the University of Bergen Bergen Norway

Abstract The Hb level during pregnancy was followed in 113 non anaemic women with uncomplicated pregnancy and birth weight of the baby above the 2 5th percentile There was an inverse correlation close to statistical significance between the birth weight of the baby and the lowest Hb level reached during pregnancy as well as the Hb level in late pregnancy (38th week) A group of seven non anaemic women with birth weight of the baby below the 2 5th percentile had a significantly higher ($p<0\ 001$) Hb level in late pregnancy than the normal group Four of these cases had a statistically significant higher Hb level already in the second trimester Trends in the reproductive history complaints in the present pregnancy as well as results of hormone assays and the condition of the baby indicated that the seven cases represented a pathological group with fetal growth retardation None of the women in the two groups were treated with diuretics All had iron supplementation in high doses

The initial aim of the present study was to define the physiological limits for haemodilution during pregnancy in our female population In the course of the study we were struck by the observation of three cases with unusually high Hb levels associated with fetal disorders intrauterine death of unknown cause oligohydramniosis with fetal distress and fetal growth retardation

The traditional clinical line of thinking has been to associate low birth weight with low Hb levels though this association has never been definitely established (1)

Data from research in the basic physiology of pregnancy on the other hand strongly indicate an inverse correlation between birth weight of the baby and Hb level of the mother Haemodilution is caused by the disproportionately greater increase of plasma volume compared with red cell volume The increase of plasma volume is correlated with the birth weight of the baby (7 12 16) and is less in women with a poor reproductive history than in normal women (9 10) In non anaemic pregnant women a low Hb level indicates a relatively high increase of plasma volume (4 13 14) Gibson demonstrated a strong inverse correlation between the lowest concentration of haemoglobin reached during pregnancy and the birth weight of the baby Some of these babies were probably abnormally small (9)

In the present study the correlation between the Hb level of the mother and the birth weight of the baby has been tested in non anaemic women with apparently uncomplicated pregnancies

SUBJECTS AND METHODS

Subjects A random series of 113 healthy women with presumptively uncomplicated pregnancies and healthy newborn was selected from our antenatal clinic during the years 1975 and 1976 Their age was 26 9±4 9 years and their height 166 7±4 8 cm Each of the women had had on the average seven blood examinations during the last 29 weeks of their pregnancy

Fifty-one women were primiparae and 67 multiparae Three had had a stillbirth in the first pregnancy but a quite normal present pregnancy with birth weight of the baby above the 10th percentile Eight cases had been delivered by vacuum extraction or low forceps and 5 by caesarean section but none because of fetal distress

The newborn had a maximum Apgar score after one minute in 103 cases and in all after five minutes

The birth weight had a mean of 3 617±449 g with a range of 2 790 g to 4 6 0 g The weights were judged in terms of gestation period sex and parity specific standards according to Bjerkedal et al (3) These standards are based on figures from the National Birth Registry which includes both normal and pathological cases As might be expected the distribution of these presumptively normal cases showed a slight tendency towards higher birth weights Fifteen were above the 90th percentile and among these were three cases above the 97 5th percentile Ten cases fell below the 10th percentile but none below the 2 5th percentile

In order to extend the study to include cases with birth weight of the baby below the 2 5th percentile as well the

Table I *Data on seven cases with birth weight of the babies below the 2 5th percentile*

Initials Height (cm)	Reproductive history	Present pregnancy	Labour delivery	Week delivered	Fetal or neonatal distress	Birth weight (g)
Z M 152	No previous pregnancy	Persistent low abdominal pain	Spontaneous start Uncomplicated	39	No	2 290
S I J 161	No previous pregnancy Six years subfertility	Anxiety neurosis	Spontaneous start Uncomplicated	40	No	2 310
G S U 172	Subfertility One uncomplicated pregnancy and labour Baby 3 4?0 g	Plasma estriol below 2 S D plasma HPL normal in the 39th week	Induction of labour Uncomplicated	40	No	2 600
V H K 157	One uncomplicated pregnancy and labour Baby 2 660 g	Uncomplicated	Spontaneous start Uncomplicated	40	No	2 3?0
A J L 168	One pregnancy with preeclampsia and fetal death	Both plasma estriol and plasma HPL below 2 S D in 38th week	Spontaneous but meconium stained liquor amnii from the start	40	Probably but good condition at birth	2 190
L R 165	First pregnancy fetal death One child with mental retardation	Plasma estriol below 2 S D plasma HPL normal in the 37th week	Caesarean section because of growth retardation Sterilization	38	Severe neonatal distress	2 100
A AA N	First pregnancy uncomplicated Baby 2 900 g Second pregnancy extrauterine	Both plasma estriol and plasma HPL below 2 S D from 30th week	Caesarean section because of growth retardation and fetal distress	37	Fetal distress but good condition at delivery	1 680

total number of deliveries at the department during the years 1975 and 1976 was screened Seven women were identified who had apparently uncomplicated pregnancies except for small for-date babies below the 2 5th percentile and who had attended our antenatal clinic where at least five blood tests had been performed under similar conditions and with the same laboratory technique as in the series of 113 cases

The mean age of the seven women was 26 4±3 5 years Data on the reproductive history the present pregnancy the labour the birth weight and the condition of the baby are given in Table I

Blood sampling and laboratory technique All women had travelled to the clinic where the examination took place between 9 a m and noon After the clinical examination the women went to the laboratory and waited about 10 min in a sitting position The blood samples were drawn from the antecubital vein after short stasis Haemolgobin was determined as cyanhaemoglobin and haematocrit by centrifugation

Haematological state and medication All had MCHC within normal limits *In those with a persistently low Hb level* additional examinations were performed MCV MCH serum iron and T I B C None of the cases showed clinical or laboratory signs of anaemia

All women received iron supplementation in daily doses of 100–200 mg Fe from early pregnancy

None of the women were treated with diuretics

Statistical methods A polynomial equation of second degree $Y=a_0+a_1x+a_2x^2$—proved useful for describing the mean values of the haemoglobin concentration in relation to the duration of the pregnancy in the above defined presumptive normal group of 113 cases with birth weight above the 2 5th percentile

Here y is the calculated value of haemoglobin concentration and x the days of duration of the pregnancy The coeffecients a_0 a_1 and a_2 were determined by the method of least squares i e in a way that best fitted the actual observations The same formula was also adjusted to each case

The comparison between this material and the seven cases with small for-date babies below the ? 5th percentile could not be based on this formula because the number of observations before day 147 was too small Instead a straight line was adjusted for the last part of the pregnancy in each case The line was characterized by the following parameters

A–Hb 221 The height of the interpolated Hb value at day 221
B The rise of the line
C Dispersion of observed values—residual standard deviation

Significant differences between the two groups were found by both the *t* test and the nonparametrical test for parameters A and B but not for C Parameters A and B

Table II *Observed and calculated mean values and standard deviation (S D) of haemoglobin concentration (Y) in normal pregnancies*

Week	Y obs	Y calc	S D obs	S D calc	*N*	Week	Y obs	Y calc	S D obs	S D calc	*N*
12	12 35	12 32	0 80	0 80	20	27	11 25	11 41	0 76	0 80	31
13	12 28	1 18	0 8	0 80	25	28	11 52	11 44	0 84	0 80	23
14	1 00	12 06	0 65	0 80	18	29	11 68	11 48	0 61	0 80	26
15	12 11	11 94	0 78	0 80	22	30	11 69	11 52	0 95	0 80	28
16	11 68	11 84	0 64	0 80	23	31	11 57	11 58	0 70	0 80	26
17	11 93	11 74	0 73	0 80	30	32	11 70	11 65	0 82	0 80	43
18	11 61	11 66	0 64	0 80	23	33	11 53	11 74	0 91	0 80	30
19	11 41	11 59	0 54	0 80	0	34	11 91	11 83	1 03	0 80	30
20	11 42	11 53	0 65	0 80	21	35	11 98	11 93	0 73	0 80	30
21	11 42	11 48	0 87	0 80	26	36	12 04	12 05	0 84	0 80	48
22	11 47	11 44	0 75	0 80	8	37	12 11	12 17	0 91	0 80	40
23	11 20	11 41	0 69	0 80	29	38	1 0	12 31	0 71	0 80	31
24	11 18	11 40	0 79	0 80	21	39	12 52	12 46	0 82	0 80	30
25	11 55	11 39	0 68	0 80	23	40	12 57	12 62	0 91	0 80	20
26	11 63	11 39	0 94	0 80	29						

were then combined in the simplest type of discrimination analysis (Armitage (1971) § 10 5)

The linear combination which gave the best discrimination was

D=A+41 B

D=interpolated Hb level day 26 i e about 38 weeks of pregnancy

RESULTS

One hundred and thirteen cases with birthweight of the baby above the 2.5th percentile Primi and multiparae were tested separately and found to give practically identical results for the parameters tested The same was true for the three women who had had a stillbirth The material is therefore treated as a single group

The mean observed and calculated haemoglobin concentrations with the respective standard deviations are shown in Table II

A definite Hb minimum was established in 101 cases An inverse correlation close to statistical significance was found between the birth weight of the baby on the one hand and the Hb minimum as well as the Hb level day 262 on the other This statistical correlation was not stronger in the cases with birthweight of the babies between the 10th and the 2 5th percentile

The correlation between the Hb level and birth weight did not improve significantly when the material was adjusted for the height and weight of the mother

Seven cases with birth weight of the baby below the 2.5th percentile The women in this group were on the average smaller than in the first group The difference however was not sufficient to account for the difference in the mean birth weight of the two groups Hormone assays were performed in 4 cases and all of them showed abnormally low levels One woman had had a first apparently uncomplicated pregnancy with a small baby The baby in the present pregnancy was still smaller One of the primiparae had persistent abdominal pain possibly of psychosomatic origin and the other suffered a severe anxiety neurosis during the present pregnancy Bahna and Bjerkedal (2) found that pregnancies complicated with neuroses are associated with low birth weight and hypoxia Also the other data in Table I indicate that these seven cases represent a pathological group compared with the 113 presumably normal cases Calculated as described previously the mean Hb level on day 262 in the pathological group was 14 12±S E (X) 0 40 and in the normal group 12 18±S E (X) 0 073 The difference is highly significant ($p<0\ 001$) both by t test and by non parametrical tests

Fig 1 shows the observed consecutive Hb levels in each of the seven cases compared with the mean and two S D levels of the 113 cases The Hb levels in a woman with the highest degree of haemodilution are shown by way of contrast This woman was perfectly healthy and gave birth to a normal baby with a birth weight between the 50th and 75th percentiles

In six of the seven cases the Hb level was higher

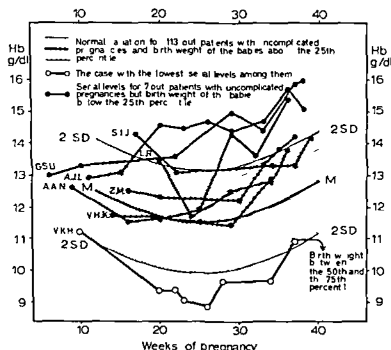


Fig 1

te pregnancy than in the non pregnant state six ht weeks after delivery

four of the seven cases the Hb level was above the two S D levels already in the second trimester

DISCUSSION

The mean Hb level of the normal group was similar to that given in other series with iron supplementation in high doses with a minimum in the second to third trimester and a significant rise towards term (15 17 20) This is in contrast to series without iron supplementation where the Hb level tends to fall or shows only a small rise towards term (5 8 21)

Our standard deviation and range are similar to those found by previous authors Liley reported a series of 114 cases with a range of 8 6 to 14 2 g/dl (13) All his cases had normal blood film serum iron I B C and folate levels and none showed reticulocytosis on iron or folate therapy It seems safe to conclude that we have to accept a high degree of haemodilution as normal

We found an inverse correlation between the birth weight of the baby and the Hb level during pregnancy in the normal group This correlation however did not reach statistical significance as in Gibson s study The reasons might be that our sampling conditions were not standardized and also that some abnormally small babies probably were included in her series (9)

Compared with the normal one our pathological group with growth retarded babies had significantly higher Hb level in late pregnancy It seems reasonable to associate this phenomenon with an inadequate increase of the plasma volume Hytten states the ability to produce a large increase in plasma volume is one of the hallmarks of a successful pregnancy (11)

In this connection it might be appropriate to mention that haemoconcentration is a frequent finding in severe hypertensive complications of pregnancy (6 18) Hypertensive complications are also associated with fetal growth retardation A reduction in plasma volume occurs during preeclampsia and eclampsia roughly in proportion to the severity of the disease (4 19) and this reduction of the plasma volume might be the common denominator for haemoconcentration and growth retardation

One might speculate whether high Hb levels already in the second trimester herald an early onset of growth retardation

Our pathological material is small but the main result is statistically highly significant and in accordance with basic elements in the physiology of pregnancy Since the collection of the material was completed we have seen five additional cases with

fetal growth retardation and abnormally high Hb levels We have also noticed a significant impact of the sampling conditions on the results After a good night s sleep and in resting position the Hb level may drop 10% or more in normal cases In cases with growth retardation the drop is not consistent and seems to require much more resting time to achieve similar results With better standardization of the sampling conditions the simple Hb test might turn out to be a useful tool for assessing the growth and wellbeing of the baby

REFERENCES

1 Auinger W N & Zeibekis N Einfluss der Anaemie auf Kindes und Placentagewicht Geburtsh Frauenheilk *37* 589 1977

2 Bahna S L & Bjerkedal T The course and outcome of pregnancy in women with neuroses Acta Obstet Gynecol *53* 129 1974

3 Bjerkedal T Bakketeig L & Lehmann E H Percentiles of birth weights of single live births at different gestation periods Acta paediat Scand *62* 449 1973

4 Chesley L C Plasma and red cell volumes during pregnancy Am J Obstet Gynecol *112* 440 1972

5 Chrisholm M A controlled clinical trial of prophylactic folic acid and iron in pregnancy J Obstet Gynecol Br Comm *73* 191 1966

6 Dieckmann W J Blood and plasma volume changes in eclampsia Am J Obstet Gynecol *32* 927 1936

7 Duffus G M MacGillivray I & Dennis K J The relationship between baby weight and changes in maternal weight total body water plasma volume electrolytes and proteins and urinary oestriol excretion J Obstet Gynaecol Br Comm *78* 97 1971

8 Fleming A F Martin J D & Stenhouse N S Pregnancy anaemia iron and folate deficiency in Western Australia Med J Aust *II* 479 1974

9 Gibson H M Plasma volume and glomerular filtration rate in pregnancy and their relation to differences in fetal growth J Obstet Gynaecol Br Comm 80 1067 1973

10 Hytten F E *In* Physiology of Human Pregnancy (ed F E Hytten & I Leitch) p 17 Blackwell Scientific Publications Oxford London Edinburgh and Melbourne 1971

11 Hytten F E Metabolic adaptations of pregnancy *In* Prevention of Handicap through Antenatal Care (ed A C Turnbull & F P Woodford) p 35 Associated Scientific Publishers Amsterdam Oxford and New York 1976

12 Hytten F E & Paintin D B Increase in plasma volume during normal pregnancy J Obstet Gynaecol Br Comm *70* 402 1963

13 Liley A W Clinical and laboratory significance of variations in maternal plasma volume in pregnancies Int J Gynaecol Obstet *8* 358 1970

14 Lund C J & Donovan J C Blood volume during pregnancy Am J Obstet Gynecol *98* 393 1967

15 Paintin D B Thomson A M & Hytten F E Iron and the haemoglobin level in pregnancy J Obstet Gynaecol Br Comm *73* 181 1966

16 Pirani B B K Campell D M & MacGillivray I Plasma volume in normal first pregnancy J Obstet Gynaecol Br Comm *80* 884 1973

17 Sjøstedt J E Manner P Nummi S & Ekenved G Oral Iron Prophylaxis during Pregnancy Acta Obstet Gynecol Scand Suppl 60 Almqvist & Wiksell Periodical Company Stockholm 1977

18 Skajaa K Variation in the cell volume of the blood in pregnancy toxemia and in labour Acta Obstet Gynecol Scand *13* 371 1979

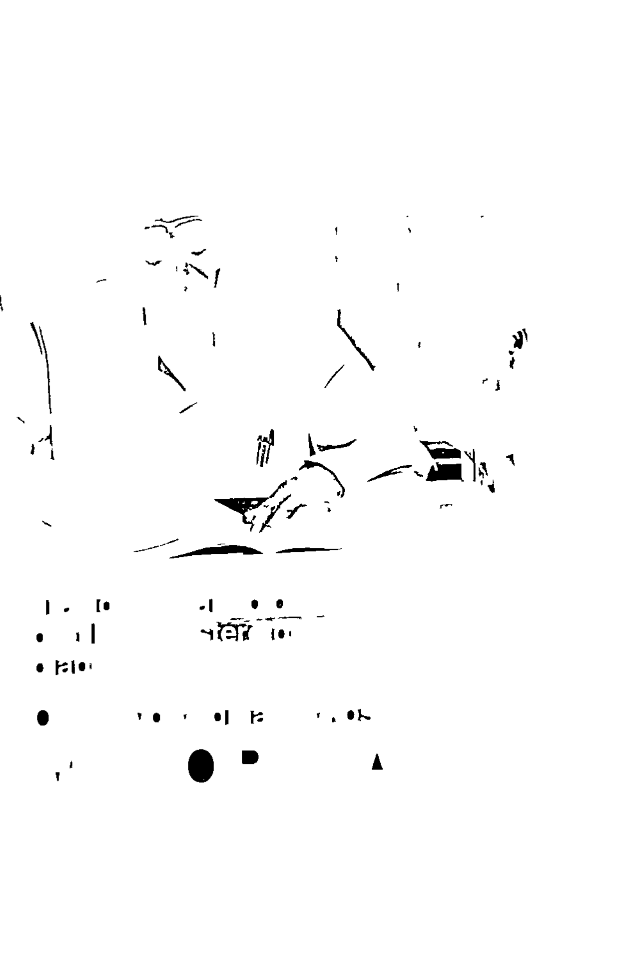
19 Soffronoff E C Kaufmann B M & Connaughton J F Intravascular volume determination and fetal outcome in hypertensive diseases of pregnancy Am J Obstet Gynecol *127* 4 1977

20 Svanberg B Arvidsson B Norrby A Rybo G & Solvell L Absorption of supplemental iron during pregnancy—A longitudinal study with repeated bonemarrow studies and absorbtion measurements *In* Absorption of Iron in Pregnancy (ed B Svanberg) p 87 Acta Obstet Gynecol Scand Suppl 48 Almqvist & Wiksell Periodical Company Stockholm 1975

21 Taylor D J & Lind T Haematological changes during normal pregnancy Iron induced macrocytosis Br J Obstet Gynaecol *83* 760 1976

Submitted for publication Dec 24 1977

Oddmund Koller
Department of Obstetrics and Gynecology
Haukeland Hospital
Norway



Acta Obstet Gynecol Scand 58 15–17 1979

MATERNAL ALCOHOL AND TOBACCO CONSUMPTION AND THEIR ASSOCIATION WITH NAUSEA AND VOMITING DURING PREGNANCY

Ruth E Little and Ernest B Hook

From the Department of Psychiatry and Beha ioral Sciences and Department of Epidemiology University of Washington GI-80 Seattle Washington 98195 and the New York State Department of Health and Birth Defects Institute Albany Medical College Albany New York 12208 USA

Abstract Nausea and vomiting during pregnancy (NVP) has been associated with favorable pregnancy outcome though little is known about factors influencing its occurrence In this study information on NVP in 10 patients at a west coast health maintenance organization was obtained Smoking and alcohol consumption before and during pregnancy were also estimated in two personal interviews during gestation In all 72% of the subjects had NVP in the first 4 months of pregnancy Smokers had significantly less NVP than non smokers (5 % vs 79%) Furthermore NVP in smokers was negatively associated with alcohol consumption before and during pregnancy with the stronger relation being for alcohol reported in the 6 months *before* pregnancy only 46% of smokers drinking more than ½ fl oz of absolute alcohol daily in this period reported NVP while 68% of smokers drinking less had NVP For non smokers there was no relation between alcohol use in any period and NVP The risk of NVP associated with pre pregnancy drinking was not related to any change in alcohol consumption after conception These results suggest an interaction between NVP smoking and reported alcohol consumption The association of favorable pregnancy outcome with NVP may be in part a reflection of moderation in maternal alcohol and tobacco use

The causes of nausea and vomiting during pregnancy (NVP) are unknown although it occurs in about 75% of gravid women (2 9 11) There are however numerous reports that NVP is a favorable prognostic sign In mothers of singleton infants the risk of abortion prior to the 20th week of pregnancy is decreased if NVP is present (2 5 9 12) Liveborn children are reported to be of greater gestational age and higher birthweight than children born to women without NVP (2)

The purpose of this paper is to report a serendipitous finding on the occurrence of NVP The phenomenon appears to be related in a complex way to alcohol and tobacco consumption not only during pregnancy but possibly in the pre conception period Alcohol and tobacco use are in turn related to infant birthweight and perinatal mortality (1 4 7 10) Therefore the association of favorable pregnancy outcome with NVP may be confounded with maternal smoking and drinking habits

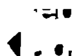
SUBJECTS AND METHODS

The purpose of the study from which these data are drawn was to determine the relationship of regular maternal alcohol use to infant birth weight Alcohol use was expressed in terms of average ounces of ethanol consumed daily This value was termed AA score Regular drinking was defined to be an AA score of 0 5 or more which is equivalent to an average of at least one one-ounce shot of 100-proof whiskey daily

Subjects in the research were obstetrical patients in the prenatal clinic of a large health maintenance organization on the west coast Nine hundred consecutive women who were paying members of the organization and who obtained prenatal care by the fourth month of gestation were contacted 90% (806) agreed to participate in the investigation The first 16? women eligible for study had an extensive personal interview in the fourth month of pregnancy covering smoking habits beverage consumption and drug and medication use AA scores for the 6 months before pregnancy and in the first 4 months of gestation were obtained The remaining 644 women participating were screened for alcohol use Sixty regular drinkers before or during early pregnancy were identified and they were also interviewed in depth

Of the ?? interviewed women ?10 were still pregnant and available for follow up in the eighth month of gestation At this time additional information on the variables noted above was obtained and the degree of nausea throughout the pregnancy determined The results described below are based on the data from these 210 women

For this report AA scores have been classified into three groups "regular" drinking for AA scores of 0 5 or more infrequent drinking for AA scores of 0 1 or less













during pregnancy used fewer anti-emetic drugs (8) It also corroborates the work of Kullander & Kallen who found a relatively low rate of NVP among smokers (5) In this sample however use of both alcohol and tobacco was necessary for the relationship with decreased rate of NVP to be evident

The relationship is more complex than it first appears Our original hypothesis was that NVP would be less frequent in women who drank or smoked regularly in early pregnancy We are somewhat at a loss to explain the fact that the hypothesis holds more strongly for pre pregnancy habits than for habits after conception and that NVP does not appear to be a significant factor in the change in alcohol use during the early months of pregnancy

In any case an alcohol–tobacco–NVP interaction has implications for fetal welfare Nausea and vomiting in early pregnancy may be a favorable prognostic sign because women who experience it are less likely to be regular drinkers and smokers Whether NVP has an influence apart from these remains to be seen

ACKNOWLEDGEMENTS

This work was partially supported by grant number AA0 174-01 from the National Institute on Alcohol Abuse and Alcoholism and by the Spencer Foundation

REFERENCES

1 Andrews J & McGarry J M A community study of smoking in pregnancy J Obstet Gynaecol Br Commonw *79* 1057–1073 197?

2 Brandes J M First trimester nausea and vomiting as related to outcome of pregnancy Obstet Gynecol *30* 4?7–431 1967

3 Hook E B Changes in tobacco smoking and ingestion of alcohol and caffeinated beverages during early pregnancy Are these consequences in part of fetoprotective mechanisms diminishing maternal exposure to embryotoxins? *In* Birth Defects Risks and Consequences (ed S Kelly et al) Academic Press New York 1976

4 Kaminski M Rumeau Roquette C & Schwartz D Consommation d alcool chez les femmes enceintes et issue de la grossesse Rev Epidem et Sante Publ *24* 27–40 1976

5 Kullander S & Kallen B A prospective study of drugs and pregnancy II Anti-emetic drugs Acta Obstet Gynecol Scand *55* 105–111 1976

6 Little R Schultz F & Mandell W Drinking during pregnancy J Stud Alc *37* 375–379 1976

7 Little R E Moderate alcohol use during pregnancy and decreased infant birth weight Amer J Pub Hlth *67* 1154–1156 1977

8 Mau G & Netter P Kaffee und Alkoholkonsum Risikofaktoren in der Schwangerschaft? Geburtsh Frauenheilk *34* 1018–1022 1974

9 Medalie J H Relationship between nausea and/or vomiting in early pregnancy and abortion Lancet *ii* 117–119 1957

10 Meyer M B Tonascia J A & Buck C The interrelationship of maternal smoking and increased perinatal mortality with other risk factors Amer J Epid *100* 443–45? 1975

11 Midwinter A Vomiting in pregnancy The Practitioner *206* 743–750 1971

12 Yerushalmy J & Milkovich L Evaluation of the teratogenic effect of meclizine in man Am J Obstet Gynecol *93* 553–562 1965

Submitted for publication Sept 7 1977

Ruth E Little Sc D
Dept of Psychiatry and Behavioral Sciences
University of Washington
Seattle Wa 98195
USA

Acta Obstet Gynecol Scand 58 19–21 1979

RED CELL 2 3 DIPHOSPHOGLYCERATE IN PREGNANCY

N E Bille Brahe and M Rorth

From the Departments of Obstetrics Sct Joseph Hospital and Clinical Chemistry Rigshospitalet Copenhagen Denmark

Abstract In normal primigravidae red cell 2 3 diphosphoglycerate (2 3 DPG) concentration was found to be increased significantly from the third month of pregnancy The 2 3-DPG concentration remained elevated throughout pregnancy Increase in the 2 3 DPG concentration leads to a decrease in the oxygen affinity of the maternal red cells The combination of low pCO and low oxygen affinity of the maternal blood facilitates the transport of oxygen as well as that of carbon dioxide across the placenta The weight of the delivered children was not significantly correlated to the 2 3 DPG changes and no significant variation of the measured variables could be detected in 9 women with abnormal pregnancies

The transport of oxygen from maternal to fetal blood during pregnancy represents a unique physiological problem The efficiency of the transport depends on the anatomical arrangement of the two vascular systems but it also depends on the difference in oxygen affinity of the two types of red cells It is therefore of special interest to investigate the factors influencing the oxygen affinity of red cells in pregnant women The intraerythrocytic concentration of 2 3-diphosphoglycerate (2 3-DPG) is important in this context Modest changes in the oxygen affinity can be expected to influence the oxygen transport from mother to fetus in contrast to the lack of a significant effect of small changes in oxygen affinity on the oxygen delivery in other physiological situations (1)

We found in a preliminary study (9) that an increase in the red cell 2 3 DPG concentration was found in pregnant women Such an increase will lead to a decrease in oxygen affinity of the maternal red cells and thereby a facilitation of oxygen transport across the placenta especially in face of the low pCO_2 which is invariably found in the blood of pregnant women (7) The present study is an extension of the preliminary study and follows a group of women during pregnancy so that a more accurate assessment of the changes can be obtained An attempt was made to correlate the measured variables with the birth weight of the babies

MATERIAL AND METHODS

Originally 60 primiparae aged 20–30 years were selected Ten of these either moved from the area or failed to attend for repeat investigation Nine women had abnormal pregnancies (praeeclampsia growth retarded fetus twins) The normal material therefore consisted of 41 women Samples were drawn after 3 7 and 8 months of pregnancy on the day of delivery and 4–5 days after delivery All women were given routine iron supplement The control group consisted of 45 non pregnant women of the same average age as the study groups none of these women received hormone therapy Blood was drawn from the antecubital vein in heparinized tubes Plasma was immediately prepared and later analysed for inorganic phosphate (3) Aliquots of whole blood was extracted as previously described (9) and analysed for 2 3 DPG (8) Standard bicarbonate was measured according to Jørgensen et al (6) Hemoglobin concentration was measured by the Cyan methemoglobin method (11) Hematocrit was measured by capillary tube centrifugation (in triplicate)

RESULTS

The hemoglobin concentration was found to decrease slightly during the first 2 trimesters whereafter it gradually increased to reach near normal values at the end of pregnancy The initial fall in the hemoglobin concentration represents a decrease in the mean red cell hemoglobin concentration since the hematocrit value remained nearly constant (Fig 1) By calculating the MCHC (cHgb/hematocrit) for each patient a significant decrease ($p<0.05$) was found from 0 to third month and from third to seventh month The standard bicarbonate concentration was found to decrease significantly reflecting the well known respiratory alkalosis prevailing from early pregnancy (Fig 2) The red cell 2 3 DPG concentration was already after 3 months of pregnancy significantly higher than in normal controls and remained so during pregnancy In contrast to our preliminary findings there was no significant change during the last two trimesters of pregnancy and the first days after delivery Finally we found in accordance with the earlier study t the

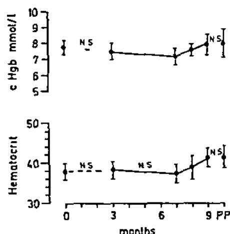


Fig 1 Hemoglobin concentration and hematocrit in venous blood during pregnancy *pp* = post partum Vertical bars indicate standard deviation (S D) N S = not significant * $p<0.05$ $p<0.01$

plasma concentration of inorganic phosphate changed only insignificantly during pregnancy but increased significantly after delivery (Fig 4)

DISCUSSION

general this longitudinal study confirmed our reliminary finding that the red cell 2 3 DPG concentration is higher during pregnancy than in normal women The increase is already significant by the third month of pregnancy and there are no further significant changes during pregnancy In the preliminary study where groups of 20 women (at 0 7 8 9 month and after delivery) were studied the 2 3 DPG increase was found to be more progressive The present study in which a group of 41 women was *followed* through pregnancy is likely to show the effect of increasing gestation more accurately The increase is probably related at least

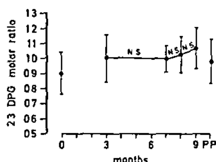


Fig 3 2 3 DPG levels in red cell during pregnancy Molar ratio=moles 2 3 DPG/mole hemoglobin tetramer Symbols as in Fig 1

partly to the respiratory alkalosis already prevailing by the third month of pregnancy (7) The 2 3 DPG increase thus neutralizes the increase in oxygen affinity caused by the low pCO In fact calculations have shown that the 2 3 DPG increase leads to a slight overshoot so that the actual oxygen affinity of the maternal blood is decreased (10) Other factors than pH changes might contribute to the 2 3 DPG increase such as hormone effects and relative anemia during pregnancy

In the present study we found no significant correlation between the 2 3 DPG concentration and the hemoglobin concentration in the pregnant women while a significant correlation (negative) between these variables was found in the group of non pregnant women in accordance with several other studies (2 5) Obviously a decrease in the oxygen affinity of the maternal blod will enhance the oxygen transport across the placenta and at the same time the respiratory alkalosis will enhance the transport of carbon dioxide from the fetus to the mother An optimal transport across placenta is

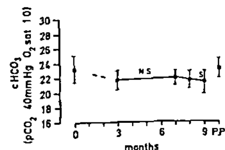


Fig 2 Standard bicarbonate levels in venous blood during pregnancy Symbols as in Fig 1

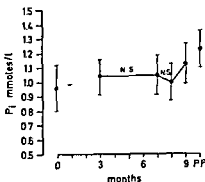


Fig 4 Inorganic phosphate concentration in venous plasma during pregnancy Symbols as in Fig 1

necessary for optimal development of the fetus We therefore tested whether or not a correlation between the oxygen unloading capacity (calculated from measured hemoglobin concentration and estimated oxygen affinity of the blood) of the maternal blood and the birth weight of the child could be found in normal pregnancies Obviously the birth weight is a variable influence by a multiplicity of other factors and it was therefore not suprising that no such correlation could be found In the abnormal pregnancies we could detect no significant difference from the normal pregnancies in the measured variables Two patients had babies that were abnormally small in none of these cases could this be explained by changes in oxygen affinity of the maternal blood

Finally we confirmed the previous finding that the inorganic phosphate concentration in plasma is increased after delivery It is likely that the pregnant woman accumulates phosphate in her body as respiratory alkalosis is known to lead to such an accumulation (4) After delivery when the acid–base status returns to normal the excess phosphate leaving the cells giving rise to an increase in the extracellular phosphate concentration It is likely that the relatively high concentration of inorganic phosphate in the organism after delivery is responsible for the maintainance of a relatively high red cell 2 3 DPG concentration

REFERENCES

1 Bille Brahe N E Kehlet H Madsbad S & Rorth M Effects of androgens on oxygen affinity in vivo and 2 3-diphosphoglycerate content of red cells in peripheral arterial insufficiency Scand J Clin Lab Invest 36 801 1976

2 Eaton J W & Brewer G J The relationship between red cell 2 3-diphosphoglycerate and levels of hemoglobin in the human Proc Nat Acad Sci 61 756 1968

3 Fiske C H & Subbarrow Y The colorimetric determination of phosphorus J Biol Chem 66 325 1925

4 Haldane J B S Wiggesworth V B & Woodrow C E The effect of reaction changes on human inorganic metabolism Proc Roy Soc B 96 1924

5 Hjelm M The content of 2 3-diphosphoglycerate and some other phosphocompounds in human erythrocytes from healthy adults and subjects with different types of anemia Forsvarsmedicin 5 219 1969

6 Jorgensen K & Astrup P Standard bicarbonate its clinical significance and a new method for its determination Scand J Clin Lab Invest 9 122 1957

7 Lucius H Gahlenbeck H Kleine K O Fabe H & Bartels H Respiratory function buffer system and electrolyte concentrations of blood during human pregnancy Resp Physiol 9 311 1970

8 Rose Z Direct determination of 2 3-diphosphoglycerate Analyt Biochem 35 177 1970

9 Rørth M & Bille Brahe N E 2 3-diphosphoglycerate and creatine in the red cell during human pregnancy Scand J Clin Lab Invest 28 271 1971

10 Rørth M & Bille Brahe N E 2 3 DPG in human pregnancy In Oxygen Affinity of Hemoglobin and Red Cell Acid Base Status (ed M Rørth & P Astrup) pp 692–696 Munksgaard Copenhagen 1972

11 Zijlstra W G & Van Kampen E J Standardization of hemoglobinometry I The extinction coefficient of hemoglobincyanide Clin Chim Acta 5 719 1960

Submitted for publication August 19 1977

N E Bille Brahe M D
Department of Surgery D
Rigshospitalet
DK 2100 Copenhagen Denmark

Acta Obstet Gynecol Scand 58 23–26 1979

THE ROUTINE USE OF ORAL PROSTAGLANDIN E_2 TABLETS FOR INDUCTION OR AUGMENTATION OF LABOUR

A P Gordon Wright T P Dutt and M G Elder

From the Department of Obstetrics and Gynaecology Charing Cross Hospital Medical School London England

Abstract The use of oral prostaglandin E_2 (PGE_2) tablets is an effective and safe adjunct to low amniotomy for the induction of labour at term Routine use of this regimen and the use of oral PGE tablets for augmentation of spontaneous labour has shown that the method is very effective in multiparous patients but much less so in primiparous patients Success or failure could not be pre dicted by the pre induction Bishop score The incidence of gastro-intestinal side effects is dose dependent but is low in multiparous patients

Oral PGE_2 has been used as an oxytocic for the induction of labour since 1971 (7) usually in combi nation with low amniotomy Prostaglandin E_2 tablets have been generally available in the U K for three years and numerous trials have been published describing their use alone (8) in combina tion with low amniotomy (12) or compared with intravenous oxytocin (5 11)

Trial studies can introduce some bias in favour of the method being tested We have therefore ret rospectively analysed the records of all patients who received oral PGE_2 tablets for the induction or augmentation of labour in our unit during a one year period to determine the situations in which the use of PGE_2 is likely to be successful and in which it is acceptable to both patient and doctor During this time there were no trials of PGE_2 tablets being conducted in the unit and obstetricians were free to choose either intravenous oxytocin or oral PGE_2 tablets as adjuncts to low amniotomy The dose regimens of both treatments had previously been standardised

PATIENTS AND METHODS

The records of 144 patients who received oral PGE_2 tablets were studied and these have been divided into 3 clinical groups

(*a*) *Low amniotomy and oral PGE_2 tablets* 80 patients in whom low amniotomy was followed immediately by oral PGE_2 tablets given in an incremental dose regimen of 0 5 mg hourly for 2 hours 1 0 mg hourly for 2 hours and 1 5 mg hourly thereafter if necessary Once adequate uterine contractions had become established the dose be ing administered at that time was maintained

(*b*) *Oral PGE_2 tablets without amniotomy* 36 patients in whom oral PGE_2 tablets were used without low amniotomy because this was contraindicated or not tech nically feasible The dose regimen was the same as that described above

(*c*) *Augmentation of labour* 28 patients to whom oral PGE_2 tablets were given for augmentation of labour

Successful induction of labour was said to have oc curred when the patient did not need intravenous oxytocin during labour

The method was said to have failed if intravenous ox

Table I *Pre induction characteristics*

	Amniotomy+oral PGE tablets		Oral PGE_2 tablets (no amniotomy)	
	Success (n=53	Failure (n=27)	Success (n=19)	Failure (n=17)
Primiparae	18	22	6	10
Multiparae	35	5	13	7
Age (years) (mean±S D)	26 8±5 6	24 9±5 4	24 8±4 8	25 4±5 3
Gestation (weeks) (mean±S D)	40 5±1 3	40 4±1 4	39 4±2 7	40 1±1 6
Bishop score (1) (mean±S D)	7 0±1 7	6 1±1 9	4 5±2 0	4 3±1 8

Table II *Percentage of cases in whom oral PGE_2 tablets were successful according to parity*
Figures in parentheses are numbers of patients studied

	Primi parae	Multi parae
Amniotomy+oral PGE_2 tablets (n=80)	45%	87 5%
Oral PGE_2 tablets (no amniotomy) (n=36)	37 5%	65%
Augmentation of labour (n=28)	56%	100%
Total (n=144)	46%	80%

ytocin became necessary either because of the side effects of oral PGE_2 tablets or because the dose regimen used did not induce adequate uterine contractions

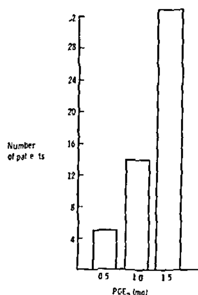


Fig 1 Hourly dose of oral prostaglandin E_2 at which vomiting and/or diarrhoea first occurred

RESULTS

The details of the patients in whom labour was induced are shown in Table I

The success rates according to parity of the three ds of using oral PGE_2 tablets are shown in e II All the methods were significantly more ıl in multiparae than in primiparae $<0 001$)

The results of the use of oral PGE_2 tablets for induction and augmentation of labour are shown in Tables III and IV respectively

Failures

The overall failure rate of the dose regimens described was 36% The reasons for failure have been grouped under four headings

(a) Side effects of PGE_2 Thirteen patients were changed to intravenous oxytocin because of vomiting four because of diarrhoea and five because they suffered from both This represents 15% of all patients who received oral PGE_2 tablets

(b) Failure because of inadequate uterine action Intravenous oxytocin was substituted for oral PGE_2 tablets in fourteen patients (10%) because of the slow progress of labour The operative delivery rate in this group was high (50%) suggesting that other factors such as cephalo-pelvic disproportion or disordered uterine action were responsible for the slow progress in many of these cases

(c) Failure because of a combination of (a) and

Table III *Results of induction of labour*
S V D =spontaneous vertex delivery LSCS=lower segment Cesarean section

	Amniotomy+oral PGE_2 tablets		Oral PGE_2 tablets (no amniotomy)	
	Success	Failure	Success	Failure
Number of patients	53 (66%)	27 (34%)	19 (53%)	17 (42%)
I D I (hours) (Mean±S D)	6 8±2 6	14 9±4 4	10 9±4 3	20 3±9 4
Duration of labour (hours) (mean±S D)	4 9±2 2	12 1±3 6	7 5±3 0	16 6±8 2
Total dose of PGE_2 mg (mean±S D)	4 6±2 9	8 7±4 5	9 8±5 3	9 4±4 0
Mode of delivery	SVD 70% Forceps 19% LSCS 2%	SVD 67% Forceps 26% LSCS 7%	SVD 89% Forceps 11% LSCS –	SVD 41% Forceps 35% LSCS 24%
Apgar score at 5 min (mean)	9 7	9 5	9 9	9 2

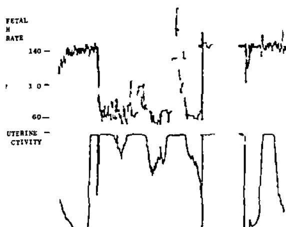


Fig 2 External cardiotocographic tracing showing fetal bradycardia associated with transient uterine hypertonus during induction of labour with oral prostaglandin E_2 tablets

(b) above There were nine patients whose contractions faded after episodes of vomiting presumably *due to rejection of the tablets*

(d) No reason No reason was apparent in retrospect for the change from PGE tablets to intravenous oxytocin in five patients

Complications

(a) Gastro-intestinal side effects The incidence was 33% and seemed to be dose related (Fig 1)

(b) Hypertonic uterine action Hypertonic uterine action occurred in three patients all of whom were primiparae One patient received a maximum hourly dose of 1 0 mg and two received 1 5 mg hourly In one patient the episode of uterine hypertonus led to transient fetal bradycardia (Fig 2) Intravenous oxytocin was subsequently used and the hypertonus did not recur Hypertonic uterine action with a rising resting pressure was noted in the other two patients but this improved on discontinuation of therapy and there were no significant changes in the fetal heart rate

DISCUSSION

There was no significant difference in the mean age or duration of pregnancy between patients who had a successful induction or augmentation of labour with oral PGE_2 tablets compared with those in whom the method failed (Tables I and IV) The mean Bishop score at the time of commencement of oral PGE_2 tablets was not significantly different in patients in whom the treatment was successful compared with those of the same group in whom it failed (Tables I and IV) The Bishop score therefore does not seem to predict success or failure when *oral PGE_2 therapy is being considered This sup*ports the findings of Karim and Sharma (8) who stated that the pre existing state of the cervix was related to the subsequent induction–delivery interval but not to the success rate of induction of labour by oral prostaglandin E_2

The most striking difference was the relatively low success rate among primiparae compared with the high success rate among multiparae (Table II) This difference is statistically significant ($p<0\ 001$) One reason for this difference is that most of the failures due to gastro-intestinal side effects were among primiparae who require a higher dose of oral PGE_2 to induce adequate uterine activity

The dose of oral PGE_2 required has been arrived at empirically The success rate has varied from 83% using a dose regimen of 0 5 mg hourly (3) to 98% *using 3 mg hourly (9) The dose regimen used* in this study is similar to those most frequently used because it strikes a balance between achieving oxytocic efficiency and an acceptable incidence of gastro-intestinal side effects An assessment of the absorption rate of PGE_2 tablets from the gastro-intestinal tract has been made by measuring the changes in plasma 15 keto PGE_2 equivalents (6) and this work suggests that the optimum frequency of tablet administration is every 45 to 60 min

The incidence of gastro-intestinal side effects is

Table IV *Results of augmentation of labour*

	Success	Failure
Number of patients	20 (71%)	8 (29%)
Age (years) (mean±S D)	26 9±5 9	24 1±4 3
Gestation (weeks) (mean±S D)	39 6±1 5	39 2±1 9
Bishop score at time of treatment (mean±S D)	7 1±2 1	6 5±2 3
Primiparae	10 (56%)	8 (44%)
Multiparae	10 (100%)	0
Treatment–delivery interval (hours) (mean±S D)	7 3±4 2	16 0±1 8
Total dose of PGE in mg (mean±S D)	4 0±2 9	6 2±4 1
Mode of delivery	SVD 70%	SVD 38%
	Forceps 30%	Forceps 62%
Apgar score at 5 min (mean)	9 7	9 7

dependent on the hourly dose of oral PGE_2 ingested Using a maximum hourly dose of 1 mg of PGE_2 solution or tablets the incidence of these side effects has been shown to be between 7% and 8% (13 14) An hourly dose of 1 5 mg raises the incidence of gastro-intestinal side effects to 15% (4) and this is illustrated in Fig 1 Higher doses lead to a further proportionate increase in side effects (9) It is therefore desirable to use oral PGE_2 tablets as an adjunct to low amniotomy only in cases where a maximum hourly dose of 1 0 mg will be effective hence selection of these patients is important

A high Bishop score usually predicts a correspondingly short induction–delivery interval However we were unable to show that the Bishop score can predict the likelihood of success in inducing labour either with or without low amniotomy This study confirms the findings of others that oral PGE tablets as an adjunct to low amniotomy are much more successful in multiparous compared with primiparous patients and that a short induction–delivery interval can be achieved with a ose regimen that does not cause excessive side ects (2 14) Primiparae and those patients requir g induction of labour without low amniotomy require higher doses of oxytocic drugs In general oral PGE_2 tablets are not suitable for these patients because gastro intestinal side effects occur before an adequate dose can be ingested and absorbed

There were three cases of transient uterine hypertonus none of which compromised the fetus This incidence is no higher than that found in spontaneous or oxytocin induced labour The induction–delivery interval particularly in multiparous patients was short confirming the findings of other studies (2 14) Assessed by the Apgar score at 5 min the use of oral PGE_2 tablets had no harmful effects on the fetus

It is our conclusion that the use of oral PGE_2 tablets as an adjunct to low amniotomy for the induction of labour at term is safe and effective particularly for multiparous patients The incidence of gastro intestinal side effects is low provided an hourly dose of 1 0 mg is not exceeded This limitation suggests that an alternative method of administration for PGE such as the extra amniotic route (10) or even intravaginal PGE_2 might be preferable An alternative route should ideally retain the simplicity of tablet taking which both patients and staff preferred to the use of intravenous infusions

REFERENCES

1 Bishop E H Pelvic scoring for elective induction Obstet Gynecol *24* 266 1964
2 Craft I Amniotomy and oral prostaglandin E_2 for induction of labour Br Med J *II* 191 1972
3 Elder M G & Stone M Induction of labour by low amniotomy and oral administration of a solution compared to a tablet of prostaglandin E_2 Prostaglandins *6* 427 1974
4 Elder M G & Stone M Induction of labour using oral prostaglandin E_2 tablets J Int Med Res *3* 300 1975
5 Elder M G Uterine action after induction of labour with oral prostaglandin E_2 tablets compared with intravenous oxytocin Br J Obstet Gynaecol *82* 674 1975
6 Gordon D Myatt L Gordon Wright A Hanson G & Elder M G Radio-immunoassay of 15 keto prostaglandin E_2 in peripheral plasma after oral administration of prostaglandin E_2 tablets used for induction of labour Prostaglandins *13* 399 1977
7 Karim S M M & Sharma S D Oral administration of prostaglandins for the induction of labour Br Med J *I* 260 1971
8 Karim S M M & Sharma S D Oral administration of prostaglandin E_2 for the induction of labour J Reprod Med 9 346 1972
9 Laverson N A & Wilson K H Induction of labor with oral prostaglandin E_2 Obstet Gynecol *44* 793 1974
10 Mellows H J Sims C D & Craft I Prostaglandin E_2 in Tylose for induction of labour in patients with a favourable cervix Proc Roy Soc Med *70* 537 1977
11 Miller J F Welply G A & Elstein M Prostaglandin E_2 tablets compared with intravenous oxytocin in induction of labour Br Med J I 14 1975
12 Thiery M Yo Le Sian A de Hemptinne D Derom R Martens G Van Kets H & Amy J J Induction of labour with prostaglandin E_2 tablets J Obstet Gynaecol Br Commonw *81* 303 1974
13 Tsakok F H M Grudzinskas J G Karim S M M & Ratnam S S The routine use of oral prostaglandin E_2 in induction of labour Br J Obstet Gynaecol *82* 894 1975
14 Visscher R D Struyk C D & Visscher H G Guidelines for the elective induction of labor with oral prostaglandin E_2 *Obstet Gynecol 49 15 1977*

Submitted for publication Feb 6 1978

M G Elder
Department of Obstetrics and Gynaecology
West London Hospital
Hammersmith Road
London W 6
England

Acta Obstet Gynecol Scand 58 27–30 1979

IS THERE A PHYSIOLOGICAL INTRAVASCULAR COAGULATION IN OBSTETRICAL CASES?

C L Arocha Pinango [1] Jesus Linares [2] Armando Cova and Paul Martinez

From [1] Instituto Venezolano de Investigaciones Cientificas (IVIC) and [2] Maternidad Concepcion Palacios Caracas Venezuela

Abstract The concentrations of plasmatic fibrinogen and its degradation products (FDPs) and the paracoagulation test using serial dilution of protamine sulphate (SDPS) were determined during the third trimester of pregnancy labor and puerperium Significant increases in the concentrations of fibrinogen and FDPs were observed throughout the process of pregnancy and birth combined with both positive and negative SDPS tests We suggest that these findings do not indicate a process of physiological DIC

Kleiner and co workers (15) have suggested that during labor a physiological DIC process exists while Hyde and co-workers (12) maintain that during normal pregnancy and puerperium there is an activation of both the clotting and the fibrinolytic mechanisms which can be detected by measuring the fibrin monomers and the amount of circulating fibrinogen/fibrin degradation products (FDPs) in the blood

In a previous paper (2) it was shown that during labor there is a high percentage of positive tests for serial dilution of protamine sulphate (SDPS) (10) both in normal and in complicated cases (pre eclampsia dead fetus premature membrane rupture etc)

This paper reports the results obtained from a group of pregnancies in which SDPS FDPs and fibrinogen concentration were determined concurrently

CLINICAL MATERIAL

Blood samples were taken from a total of 311 women 30 normal non pregnant women used as controls 4? in the third trimester of pregnancy 112 during normal labor and 1?7 during the first 48 hours post partum

None of the cases showed any hemorrhagic complication during pregnancy delivery or puerperium During labor four samples were taken at 3-hourly intervals starting at the onset of the initial uterine contraction For the series during puerperium three samples were taken at 1? ?4 and 48 hours

LABORATORY METHODS

Citrated plasma Blood was obtained by clean venipuncture and mixed 9 1 with 0 5 ml of 3 2% sodium citrate in 10% epsilon amino caproic acid The plasma was separated by centrifuging the blood immediately at 3 000 r p m for 10 minutes Tests were performed the same day when possible otherwise the samples were frozen at −?0°C All syringes tubes and caps were plastic disposable

Serial Dilution Protamine Sulphate (SDPS) test was performed according to the method described by Gurewich & Hutchinson (10) using protamine sulphate (Roche)

Fibrinogen/Fibrin Degradation Products (FDP's) Serum was obtained by mixing v/v citrate plasma with a solution of calcium/thrombin (? 5 U ml in 0 025 M CaCl) The mixture was incubated at 37°C for 30 minutes The clot was separated and kept Merskey s haemagglutination inhibition test was performed (TRCHII) (18) on the remaining serum

Fibrinogen concentration was determined by the clot weight method of Ingram (13) using the clot obtained from the above procedure

RESULTS

The results obtained for the fibrinogen FDPs and SDPS test during the third trimester of pregnancy labor and puerperium are shown in Figs 1 and 2 The fibrinogen and FDPs levels are expressed as mean plus standard deviation the SDPS test as the percentage of positive tests The total group has been subdivided into two series those with SDPS positive and negative respectively

None of the non pregnant controls were SDPS positive During the third trimester of pregnancy on the other hand 37% of the women had a positive SDPS test The percentage had dropped to 11% at the onset of labor but rose to a peak of 27% during the period of 3–6 hours during labor Thereafter the percentage dropped again until the first 12 hours of puerperium when there was a still higher peak of 41% SDPS positive followed by another decline during the period of 12 to 48 hours of puerperium

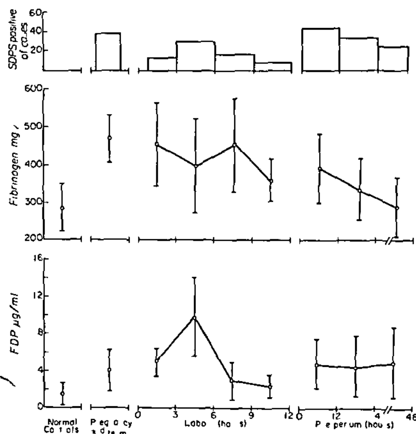


Fig. 1. Fibrinogen and FDPs compared with the incidence of positive SDPS tests.

Statistical analysis of the SDPS negative series showed that the values for fibrinogen and FDPs levels during the third trimester of pregnancy (320.3 mg% and 3.2 µg/ml) were significantly higher than in the control group (276.0 mg% and 1.07 µg/ml). Both the fibrinogen levels and the FDPs rose to somewhat higher values during labor; these values were maintained all through puerperium (Fig. 2).

In the SDPS positive series the increased levels of fibrinogen and FDPs during the third trimester of pregnancy were more marked. Fibrinogen reached a level of 470.4 mg% and FDP 4.19 µg/ml. The high level of fibrinogen was maintained during labor, but as puerperium progressed the level dropped until the period of 24–48 hours, when the value (297.8 mg%) was less than that (361.7 mg%) for the SDPS negative women during the same period.

During labor and puerperium, FDPs were maintained at levels similar to those of pregnancy with two exceptions. In the 9–12 hour period, 2 out of 35 cases had a positive SDPS test with very low values of FDPs (3.8 and 1.7 µg/ml). In the 3–6-hour period only 6 out of 32 cases had a positive SDPS; their mean FDP was 10.8 µg/ml, but 5 of them gave titers as high as 13.6 µg/ml.

Comparing the variations in the group for fibrinogen and FDP, it was observed that in the series with positive SDPS tests there were correlation in the periods 3–6 hours from labor ($r = -0.42$) and 24–48 hours of puerperium ($r = -0.76$). In the rest of the group there was no correlation between the two parameters.

DISCUSSION

The 38% incidence of positive SDPS during the third trimester of pregnancy found in this study agrees with the observations of Hyde (12). During labor, the percentage of positive SDPS varied in the period of 3–6 hours (27%), diminishing as expulsion approached. These results corroborate those reported by us in a previous paper (2). A renewed increase of positive SDPS tests (41%) was observed during the first hours of puerperium and the percentage remained elevated up to 48 hours post partum.

Those authors who, like us, have used Merskey's method (18) differ somewhat concerning the presence of FDP during pregnancy and puerperium. Hahn (11) and Woodfield (21) reported an increase

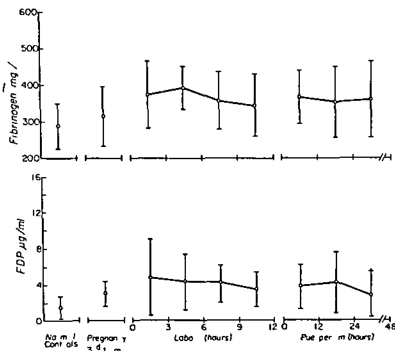


Fig 2 Variations of fibrinogen and FDPs throughout pregnancy labor and puerperium in the SDPS negative cases

in FDP levels during pregnancy while Bonnar (4) did not observe any change until the onset of labor Hyde (12) using a different technique observed an increase in the FDP level (4 µg/ml) in both pregnancy and puerperium Kelner and co-workers (15) found FDP values within the normal range during labor while in the immediate postpartum an increase was observed by Hyde (12) Statistically significant increases in FDP levels during late labor and puerperium were found by Hahn (11)

Kleiner et al (15) did not observe any significant changes in fibrinogen values during labor compared with pregnancy In the puerperium Kleiner (15) and Bonnar (6) found a significant decrease in the first 4 hours postpartum while Nilsson (19) reported that the level of fibrinogen remained unchanged during the first 4 days after delivery

In this study fibrinogen and FDPs were high in both series (SDPS positives and negatives) during the various stages The statistical analysis showed only a slight correlation between the variations of fibrinogen and degradation products in the period 24–48 hours of puerperium ($r = -0\ 76$) This suggests that the circulating FDPs do not derive from the lysis of plasmatic fibrinogen which would be expected if one accepts that the fibrinolytic activity of the plasma is diminished during pregnancy and labor (3 4 5)

No clear explanation has been found for the production of FDPs in obstetrical cases The increase has been associated with the most varied mechanisms such as the increase in the active intimal surface area subsequent to the vasodilatation in late pregnancy (20) venous obstruction of the lower limbs (22) an extravascular contribution from fibrinolysis of growing tissues (7 12) the release of thromboplastin in the bloodstream from abnormal placental damage (21) and changes in the hormonal secretion of the placenta during labor (3)

Some authors have shown that even in normal placentas there are fairly large amounts of fibrin deposits (8 9) but it has also been reported that the uterus is a major source of plasminogen activators (17) that could induce the lysis of the fibrin deposited in the placenta Abildgaard & Uszynski (1) have reported that the placenta is rich in inhibitors of the fibrinolytic system that could prevent such a lysis Based on those findings it might be argued that if both systems are balanced then the level of FDPs during pregnancy and labor would be normal or low if they were produced at uterine level

However since there are many cases with a high incidence of elevated FDPs it seems that an imbalance exists between the two systems with the lytic phenomenon occurring predominantly at the placenta But it is equally conceivable that circulat

ing FDPs are produced by lysis of the deposited fibrin by proteases other than plasmin as already reported (14 16)

The presence of fibrin monomers in the circulation as determined by SDPS tests is not constant and the variation does not seem to be related to the uterine activity during labor

The activity developed by the myometrium increases as labor progresses and it is possible that such an increase of uterine tone could limit the passage of the fibrin monomers and the FDP formed at placental level which would explain the drop in FDPs and the decreased incidence of positive SDPS during the last stages of labor

The increased incidence of positive SDPS tests during puerperium which progressively diminished could well be a result of the local activation of the hemostatic and fibrinolytic mechanisms which occur in the uterus at the moment of placental separation (6) However it must be noted that this phenomenon was not constant in the present study

In view of the circumstances discussed above we not feel that it is possible to relate either the positive SDPS tests or the high values of FDPs as an expression of a physiological DIC in obstetrical cases as has been previously suggested

ACKNOWLEDGEMENT

We wish to acknowledge the technical assistance of Lic G Montilla G Lopez and S Rodriguez and also Mr A Vielma from the Banco Mercantil y Agricola of Caracas and Dr S Gorzula for the statistical analysis

REFERENCES

1 Abildgaard U & Uszynski M Separation and characterization of two fibrinolytic inhibitors from human placenta Thromb Diath Haemorrh 25 580 1971
2 Arocha Pinango C L Linares J Cova A Martinez P Montilla G & Rodríguez S Intravascular coagulation in obstetrics serial dilution protamine sulfate test throughout labor Am J Obstet Gynecol 124 18 1976
3 Åstedt B Fibrinolytic inhibitors in human retroplacental blood Acta Obstet Gynecol Scand 53 227 1974
4 Bonnar J Davidson J F Pidgeon C F McNicol G P & Douglas A S Fibrin degradation products in normal and abnormal pregnancy and parturition Br Med J iii 137 1969
5 Bonnar J McNicol G P & Douglas A A Fibrinolytic enzyme system and pregnancy Br Med J iii 387 1969
6 Bonnar J Prentice C R N McNicol G P & Douglas A S Haemostatic mechanism in the uterine circulation during placental separation Br Med J ii 564 1970
7 Das P C Allan A G E Woodfield D C & Cash J D Fibrin degradation products in sera of normal subjects Br Med J ii 718 1967
8 Frigoletto F Tullis L J Reid D E & Hinman J Hypercoagulability in the dysmature syndrome Am J Obstet Gynecol 11 867 1971
9 Fox H White infarcts of the placenta J Obstet Gynaecol Br Commonw 70 980 1963
10 Gurewich V & Hutchinson E Detection of intravascular coagulation by a serial dilution protamine sulfate test Ann Int Med 75 895 1971
11 Hahn L On fibrinolysis and coagulation during parturition Acta Obstet Gynecol Scand Suppl 28 1974
12 Hyde E Joyce D Gurewich V & Flute P T Intravascular coagulation during pregnancy and the puerperium J Obst Gynaecol Br Commonw 80 1059 1973
13 Ingram G I C The determination of plasma fibrinogen by the clot weight method Biochem J 51 583 1952
14 Johnson A J & Merskey C On the origin of the proteolytic activity responsible for the release of fibrinogen fibrin related antigen in vitro Scand J Haematol Suppl 13 87 1971
15 Kleiner G J Merskey C Johnson A J & Markus W B Defibrination in normal and abnormal parturition Br J Haematol 19 159 1970
16 Latallo Z Teysseyre E Wegrzynowicz Z & Kopee M Degradation of fibrinogen by proteolytic enzymes Scand J Haematol Suppl 13 15 1971
17 McKay A V P Das P C Myerscough P R & Cash J B Fibrinolytic components of human uterine arterial and venous blood J Clin Pathol 20 727 1967
18 Merskey C Lalezari P & Johnson A A rapid simple sensitive method measuring fibrinolytic split product in human serum Proc Soc Exp Biol 131 871 1969
19 Nilsson I M & Kullander S Coagulation and fibrinolytic studies during pregnancy Acta Obstet Gynecol Scand 49 363 1967
20 Winner W Role of placenta in systemic circulation Obstet Gynecol Surv 20 545 1965
21 Woodfield D G Cole S K Allan A G E & Cash J D Serum fibrin degradation products throughout normal pregnancy Br Med J ii 665 1968
22 Wright H T Osborn S B & Edmonds D G Flow of venous blood in leg during pregnancy Surg Gynecol Obstet 90 481 1950

Submitted for publication Sept 11 1977

C L Arocha Pinango
Laboratorio de Fisiopatologia
I V I C -Apartado 1827
Caracas 101
Venezuela

Acta Obstet Gynecol Scand 58 31–35 1979

THE AETIOLOGY AND OUTCOME OF ABRUPTIO PLACENTAE

M E L Paterson

From the Birmingham Maternity Hospital Edgbaston Birmingham England

Abstract A series of 193 cases of abruptio placentae in a hospital population of 35 217 is described This is an incidence of 0 55% In the series both age and parity but not pre eclampsia or anaemia are significant associated factors The recurrence rate of abruptio placentae was 5 6% There were no maternal deaths and the perinatal mortality was 35% Epidural analgesia does not abolish the pain of the abruptio placentae in spite of abolishing the pain of labour

The usually quoted incidence of recurrent abruptio placentae is 17 3% (7) As it appeared to us that this figure was rather high a retrospective study was made of all patients with an abruptio placentae delivered at the Birmingham Maternity Hospital

MATERIAL AND METHODS

The period of study was from September 1968 until December 1975 A diagnosis of abruptio placentae was based on the finding of a retroplacental clot and the disruption of the underlying placental tissue All patients of less than 28 weeks gestation were excluded from the survey The association between abruptio placentae and age parity anaemia and pre-eclampsia were investigated together with the maternal and fetal outcome

The management of cases of abruptio placentae remained essentially the same throughout the period of review The aim was to deliver the patient as soon as possible and to give adquate transfusion of blood and any necessary clotting factors As a rule if the fetus was of 34 weeks gestation or more alive and vaginal delivery not imminent then a caesarean section was performed A conservative approach was adopted only in mild cases where it was felt that the fetus would stand little chance of surviving if delivered immediately

The central venous pressure was monitored in all severe cases and a full coagulation screen performed Epidural analgesia for labour was given only to those patients who had normal clotting factors and who had only a mild abruptio placentae

RESULTS

the seven year period 35 217 patients were delivered of whom 193 (0 55%) had an abruptio placentae The incidence of abruptio placentae by gravidity and age is shown in Table I

In the series 103 patients had a total of 253 completed pregnancies prior to the one in which the abruptio placentae occurred Fifty five (22%) of these pregnancies ended in abortion and ten in abruptio placentae (4%)

Eighty-one of the women had 90 pregnancies of known outcome subsequent to that complicated by the abruptio placentae Of these pregnancies six ended in abortion (6 7%) and five in abruptio placentae (5 6%)

Only eight patients were anaemic (Hb <10 5 g per 100 ml) before the abruptio placentae occurred and only one of these had a low serum folate It should be noted however that only patients with a haemoglobin of less than 10 5 g per 100 ml had a serum folate assay performed

Sixteen normally normotensive patients had a blood pressure of 140/90 mmHg or greater on two occasions or more A further six also had peripheral oedema and five more had oedema and proteinuria The diagnostic criteria of Gemmell et al (4) were adopted so that this series could be directly compared with previous ones On this basis only 5 7% of patients had pre eclamptic toxaemia and a further 8 3% had gestational hypertension

Table I *Incidence of abruptio placentae by gravidity and age*

	Gravidity			
Age	0	1	≥2	Total
<25	43/8 391 0 51%	19/4 081 0 47%	9/1 565 0 57%	71/14 037 0 52%
25–29	20/4 690 0 43%	21/4 565 0 46%	11/2 944 0 37%	5 /12 199 0 43%
30–34	7/1 350 0 52%	11/1 832 0 60%	24/2 355 1 0?%	42/5 337 0 76%
35+	4/546 0 73%	5/697 0 72%	18/1 714 1 05%	27/2 957 0 91%
Total	74/14 977 0 49%	56/1 175 0 50%	62/8 578 0 7?%	

Table II *Correlation of gestation against fetal outcome*

Figures in parentheses are the number of cases with an audible fetal heart at the time of admission

	Fetal outcome			
Gestation	Intrauterine death	Neonatal death	Survived	Total
28–32	19 (4) 55 8%	7 20 8%	8 23 4%	34
33–36	24 (5) 31 2%	5 6 5%	48 62 3%	77
37–40	8 (1) 11 0%	1 1 4%	64 87 6%	73
40+	2 (1) 22 2%	1 11 1%	6 66 7%	9
Total	53 (11) 27 5%	14 7 3%	126 65 3%	193

There were no maternal deaths and only one case of dis ascular coagulation
ered 196 babies of whom 68
es (28%) fetal death occurred
were 14 neonatal deaths (7%)
on between the gestation at which
placentae occurred and fetal outcome
Table II The gestational age was based
sessment made by either the paediatrician
nologist

any retrospective study it is difficult to be
tain of the accuracy of the assessment of the degree of severity of the abruptio placentae The patients have therefore been divided into three
oups according to the amount of blood trans
ed The severity of the abruptio placentae was
correlated with fetal outcome (Table III)

n 151 out of 193 cases the abruptio placentae
a prior to established labour In 42 cases
%) the patient was in established labour at the
the abruptio placentae Sixteen of these
had epidural analgesia but eleven of them
d of severe continuous lower abdominal
ite abolition of the pain of labour Of the
s who did not have any continuous pain
the second stage of labour and there
aled loss as well as the retroplacental
patient had a *mixed* haemorrhage and
clot was only 50 ml
of 42 patients whose abruptio placentae occurred during labour there were four perinatal deaths (Table IV)

The mode of delivery is detailed in Table V The caesarean section rate was 27% If one considers only those cases who had an audible fetal heart at the time of admission the caesarean section rate was even higher at 38%

There were six babies with major congenital central nervous system abnormalities (3 1%)

DISCUSSION

The incidence of abruptio placentae in the series was only 0 55% This is much lower than the incidence reported by Hibbard & Jeffcoate in 1966 (1 17%) and Lunan in 1973 (1 3%) but it is similar to that reported by Douglas et al in 1953 (0 55%) Paintin in 1962 (0 7%) and Golditch & Boyce in 1970 (0 46%) The variations in incidence of abruptio placentae is probably explained by a variation in the diagnostic criteria and also the hospital population may have differed considerably

From the data in Table I it would appear that both age and parity are important aetiological factors Considering each gravidity group separately the data suggests that the proportions of abruptio placentae are higher in the older age groups A chi squared test on the frequencies shows a statistically significant difference ($p<0.01$) between the four age groups for those women of gravida two or more However there is no statistically significant difference for the primigravid or secundigravid groups The data suggests the effect of age interacts with gravidity to some extent In particular the effect of age is most pronounced where gravidity is

Table III *Correlation of severity of abruptio placentae against fetal outcome*

	Fetal outcome			
Severity of abruptio placentae	Intrauterine death	Neonatal death	Survived	Total
No blood transfusion	5 7 2%	1 1 4%	63 91 3%	69
1–2 units of blood transfused	24 28 9%	10 12 0%	49 59 0%	83
More than 2 units of blood transfused	24 58 5%	3 7 3%	14 34 1%	41

Table IV *Perinatal deaths of those patients who had intra partum abruptio placentae*

Case	Time of death	Gestation in weeks	Epidural	Summary
1	Intra uterine	30	No	Anencephalic
	Intra uterine	38	No	Massive abruption before second stage—Ventouse Resuscitation failed
3	Neonatal	40	Yes	Second stage Acute fetal distress and bleeding P V Died at 30 hours
4	Neonatal	39	Yes	Second stage Acute bleed Satisfactory at birth Died from pulmonary haemorrhage 3 days

high Alternatively for women in the older age groups the proportion of abruptio placentae in eases with gravidity but this is not apparently true for the younger age groups There is nothing in the current data to suggest that the risk of abruptio placentae increases linearly with age Instead the risk seems to start increasing at about the age of 30 although this also varies with gravidity

Hibbard & Jeffcoate (7) Pritchard et al (14) and Paintin (11) showed that the association was with parity and not age The data in our series contradicts their finding and it would appear that women aged 30 or above are more likely to have an abruptio placentae and this is still true in the various gravidity sub groups

The incidence of spontaneous abortion in pregnancies prior to the abruptio placentae (21 8%) is three times our normal abortion rate This confirms the findings of others which indicated that women with a history of pregnancies complicated by abortion were more likely to suffer abruptio placentae (6)

It is interesting that the abortion rate in pregnancies subsequent to the abruptio placentae was 6 7% which is similar to the general hospital incidence

Abruptio placentae recurred in 5 6% of our patients This is similar to the incidence reported by Paintin (1962) which was 7% but lower than that reported by Pritchard et al in 1970 (11%) and Hibbard & Jeffcoat in 1966 (17 3%) The latter calculated that a patient who had had an abruptio placentae was 15 times more likely to have a recurrence This compares with a tenfold increase in our present series

Only 5 7% of the patients in the series had pre eclampsia and a further 8 3% had gestational hypertension This is no higher than our general hospital population (13% have either pre-eclampsia or gestational hypertension) It would therefore seem that pre-eclampsia and gestational hypertension are insignificant causes of abruptio placentae This confirms the findings of Hibbard & Jeffcoate (7) who reported an incidence of pre-eclampsia of 6 12% It should however be remembered that Pritchard et al in 1967 found a 47% incidence of hypertension in cases of abruptio placentae which was five times their normal incidence of hypertension and Golditch in 1970 reported a 20% incidence of pre-eclampsia

There were no maternal deaths in the series which compares favourably with previous series Tennant (15) reported five maternal deaths out of a total of 162 cases Hibbard & Jeffcoate (7) reported one maternal death out of 506 cases There was only one of disseminated intravascular coagulation which is again much lower than previous series Hibbard & Jeffcoate (7) reported a 20% incidence of coagulation failure This almost certainly reflects a general improvement in obstetric care particularly the adequate transfusion of blood and any necessary clotting factors as soon as the abruptio placentae is recognised We have found that a central venous pressure catheter is extremely helpful in severe cases supporting the view held by O Driscoll & McCarthy (10) and Muldoon (9)

Table V *Mode of delivery*

Type of delivery	Total number	Intra uterine deaths	Neo-natal deaths
Spontaneous vertex	105	50	7
Instrumental	24	1	2
Breech	11	[illegible]	3
Caesarean section	53	1	1

The perinatal mortality rate (35%) again compares favourably with previous series Tennant (15) reported a perinatal mortality rate of 87% Hibbard & Jeffcoate (7) reported a rate of 50 5% Golditch & Boyce (5) reported a rate of 30% Blair (1) reported a mortality rate of 55% and Lunan (8) reported a rate of 38% The fall in the perinatal mortality rate is in part due to the general improvement in obstetric care and early admission to hospital it is of interest to note that the lowest perinatal mortality rates were reported in series in which there was a high caesarean section rate Lunan (8) reported a caesarean section rate of 12 6% and acknowledges that a more liberal use of caesarean section could have resulted in an improved fetal survival He suggested that if the fetus was judged to be of 2 00 kg or more in weight and delivery not imminent then a caesarean section should be performed Golditch & Boyce (5) who had a caesarean section rate of 22 3% suggested that if the fetal heart was audible caesarean section should be performed immediately in those patients ho had a moderate or severe abruptio placentae ey were able to demonstrate that there was a rong correlation between the diagnosis–delivery interval and fetal survival in their moderate and severe groups The caesarean section rate in our series was 27% and there was only one neonatal death There were also five intrauterine deaths that might have survived if a caesarean section had been performed There is a considerable improvement in fetal outcome after 33 weeks gestation (see Table II) and we therefore suggest that a caesarean section should be performed in those patients of 33 weeks gestational age or more unless vaginal delivery is imminent The opposite view was taken by Porter (12) 2 5% caesarean section rate and Hibbard & Jeffcoate (7) 8 7% caesarean section rate who felt that the increase in fetal salvage did not justify a large increase in the numbers of caesarean sections Since their series were published the care of the neonate has improved considerably so we feel that we can justify a more active approach

There is a definite correlation between fetal outcome and severity of the abruptio placentae (Table III) There were only six (8 7%) perinatal deaths in those patients who did not require a blood transfusion but even in those patients who required three pints of blood or more 14 (34%) infants survived It would seem therefore that even if the patient has had a large abruptio placentae the fetus has a reasonable chance of survival provided delivery is expedited

We were particularly interested in those patients with epidural analgesia who had an abruptio placentae during labour It would be reasonable to suppose that the epidural would relieve not only the painful uterine contractions but also the pain of the abruptio placentae However in the majority of cases this did not appear to happen Those patients who did not have any pain were either in the second stage of labour or only had a small retroplacental clot It would therefore appear that epidural analgesia does not mask the pain of an abruptio placentae in an otherwise established epidural block This is difficult to explain but the most likely explanation is that there is a gradation of effectiveness of blocking transmission of impulses within individual axons by local analgesics and that an increase in the intensity or frequency of stimuli of the nerve endings can overcome an apparently established block (2)

The incidence of congenital malformations (3 1%) is high when compared with the general hospital population (1 3%) The incidence is exactly the same as that found by Hibbard & Jeffcoate (7)

ACKNOWLEDGEMENTS

I would like to thank Dr J Selwyn Crawford for his assistance in preparing this manuscript and Dr Paul Davis for the statistical analysis

REFERENCES

1 Blair R G Abruption of the placenta J Obstet Gynaecol B Commonw *80* 24? 1973
2 Crawford J S The epidural sieve and M B C (Minimal Blocking Concentration) An hypothesis Anaesthesia *31* 1278 1976
3 Douglas R G Buchman M I & Macdonald F A Premature separation of the normal situated placenta J Obstet Gynaecol B Emp *62* 712 1955
4 Gemmell A A Logan W P D & Benjamin V The incidence of toxaemia J Obstet Gynaecol Br Emp *61* 458 1954
5 Golditch I M & Boyce N E Management of abruptio placentae J Am Med Assoc *212* 288 1970
6 Hibbard B M & Hibbard E D Aetiological factors in abruptio placentae Br Med J *2* 1430 1963
7 Hibbard B M & Jeffcoate T N A Abruptio placentae Obstet Gynecol *27* 155 1966
8 Lunan C B The management of abruptio placentae J Obstet Gynaecol Br Commonw *80* 120 1973
9 Muldoon M J The use of central venous pressure

monitoring in abruptio placentae J Obstet Gynaecol Br Commonw *76* 725 1969
10 O Driscoll K & McCarthy J R Abruptio placentae and central venous pressure J Obstet Gynaecol Br Commonw *73* 973 1966
11 Paintin D E The epidemiology of ante partum haemorrhage J Obstet Gynaecol Br Commonw *69* 614 1962
12 Porter J Conservative treatment of abruptio placentae Obstet Gynecol 15 690 1960
13 Pritchard J A & Bretten A L Clinical and laboratory studies on severe abruptio placentae Am J Obstet Gynecol 97 681 1967
14 Pritchard J A Mason R Corley M & Pritchard S Genesis of severe placental abruption Am J Obstet Gynecol *108* 27 1970
15 Tennant R A The management of hypertension in accidental haemorrhage of pregnancy Obstet Gynecol *14* 665 1959

Submitted for publication September 7 1977

M E L Paterson M B Ch B M R C O G
The Birmingham Maternity Hospital
Edgbaston Birmingham England

Acta Obstet Gynecol Scand 58 37–40 1979

PERINATAL DEATH DUE TO ABRUPTIO PLACENTAE IN AN AFRICAN CITY

Richard L Naeye [1] Nebiat Tafari and Charles C Marboe

From the [1]Department of Pathology M S Hershey Medical Center The Pennsylvania State University College of Medicine Hershey Pennsylvania 17033 USA and the Ethio-Swedish Pediatric Clinic Addis Ababa University Faculty of Medicine Addis Ababa Ethiopia

Abstract Abruptio placentae was a common cause of perinatal death in Addis Ababa Ethiopia in 1974–1975 with a frequency of 5 5/1 000 births The disorder had its peak frequency at term No abnormalities were found in the placentas to explain the placental abruptions but there were other clues to their genesis There was a strong association of the fatal abruptions with severe poverty in the mothers These poor mothers were both undernourished and malnourished during pregnancy Their fetuses and neonates who died had multiple evidences of undernutrition including a relative undergrowth of adrenals spleens and livers and a relative acceleration of lung maturation These findings support observations in more prosperous nations that poor nutrition of the gravida may have an important role in the genesis of abruptio placentae

A recent study found abruptio placentae to be the fourth most common cause of perinatal death in Addis Ababa Ethiopia with a frequency of 5 5/1 000 births (9) The frequency is nearly the same in U S ities but it is far from certain that the pathogenesis of the disorder is the same in the two nations In the U S about 20% of such deaths are due to cigarette smoking which causes a selective necrosis in the decidua basalis at the margin of the placenta and another 10% are caused by large placental infarcts (8) Very few women in Addis Ababa use tobacco in any form and the frequency of infarcts in their placentas has not been determined Poor gestational nutrition might play a role in abruptio placentae in both nations Most women in Addis Ababa are both undernourished and malnourished during pregnancy while suboptimal pregnancy weight gain is a common feature of abruptio placentae in the USA (1 8)

The present study searched for the causes of abruptio placentae in Addis Ababa by analyzing data from a large study of pregnancies in that city

MATERIALS

A study of perinatal mortality was undertaken in Addis Ababa Ethiopia in 1974–1975 in the hospitals and clinics affiliated to the Addis Ababa University Faculty of Medicine About 40% of the births in the city take place in these facilities which serve all segments of the population Sixty six stillbirths and twenty neonatal deaths were placed in the abruptio placentae category when inspection showed an adherent retroplacental clot with depression or disruption of the underlying placental tissue or when there were otherwise classical clinical findings including external or occult bleeding increased firmness of the uterus and death between 20 weeks of gestation and the twenty eighth postnatal day with evidence of hypoxia including aspirated squames and petechiae on the surface of the visceral organs All of the infants had postmortem examinations Abruption cases that were the consequence of severe preeclampsia or eclampsia were placed in another diagnostic category and excluded from the present analyses

The pregnancies that ended with fatal abruptions were compared with 568 successful pregnancies selected to be representative of the delivery population These controls were comprised of the first ten deliveries after 8 AM each day that produced infants who survived the neonatal period Hospital and clinic records in conjunction with a detailed maternal interview and physical examination on the day after delivery provided 124 medical demographic and other items of information for analysis on most of the cases The information collected included durations of pregnancy based on a church calender well known to most women mother's education size and sources of income specific expenditures for food water and other items place and duration of residence housing density tribe religion details of employment facilities for excreta disposal sources of water age of first marriage and duration and status of marriages

Data were also collected on maternal age prior obstetrical history wanted/unwanted status of the pregnancy efforts at contraception abortifacients gestational hypertension peripheral edema vaginal bleeding hydramnios jaundice parasites venereal diseases including serologic tests for syphilis other specific disorders during gestation number of visits for prenatal care blood hemoglobin values blood groups leukocyte counts and medications taken during pregnancy Information was

Table I *The influence of primary maternal and family factors on perinatal mortality rates due to abruptio placentae*

Eth $2 05=US $1 00

	Perinatal mortality (rate/1 000 births)	
Family income in Eth $/month		
None	37 0	$P<0\ 001$
1–140	5 8	
141–800	1 5	
Over 800	0	
Mother had prenatal medical care		
Yes	3 2	
No	11 3	
Maternal diastolic blood pressure during labor		
Under 70 mmHg	8 6	$P<0\ 004$
71–80	3 9	
81–95	2 1	
Over 95	2 7	

collected on details of labor and delivery fetal dis Apgar scores infant blood groups and the clinical e of the neonate and mother after delivery

each well preserved case body and organ measurements were calculated in percent of mean normal autopsy values as published by Gruenwald and Minh (2) A mean percent of normal published values was then calculated for each organ or body measurement for the group as a whole Infants of multiple births and those with major congenital anomalies or known diabetic mothers were excluded from the study Well preserved lungs were histologically graded for their stage of maturity by the system of Platt (5 6) Four specially trained technicians reviewed microscopic sections from the 80 well preserved placentas of the fatal abruption cases and from the 507 placentas available from the successful pregnancies Nonroutine abnormalities were checked by the present senior author

STATISTICAL METHODS

Details have recently been published on the statistical methods used to determine which of the many variables were primarily related to the abruptio placentae fatalities (7) Primary variables were judged to be those that had a significant influence on the mortality rates without being dependent on other variables First the frequency of each variable in the fatal cases was compared with its frequency in the controls using the chi square test in two-way contingency tables This resulted in a shortened list that included both primary and secondary variables (Table I) Cases in which observations were missing for a particular variable were excluded only in analyses involving that variable so that the statistical analyses were based on the entire data set

A log linear model analysis of contingency tables was carried out on the smaller set of variables The interrelationships of all possible pairs of these variables were then determined on the frequency of perinatal mortality due to abruptio placentae Tests for zero three factor interactions were performed in the resulting 3 way contingency tables Variables which had a significant influence on the frequency of fatal abruptio placentae without being dependent on other variables are found in Table I

RESULTS

The frequency of the perinatal deaths due to abruptio placentae was 5 5/1 000 births and their peak was at term (Fig 1) The organs of the infants who died were growth retarded Adrenals spleens livers and hearts were more affected than bone growth as reflected in body length The brains were not growth retarded (Fig 2) Fetal lung maturation was accelerated at all gestational ages in the fatal abruption cases by comparison with U S controls (Table II) The only placental abnormality detected in the abruptio cases was an increased frequency of infarcts under 3 cm in diameter so called small infarcts (8) They had a frequency of 12% in the abruptio cases and only 1% in the surviving controls ($P<0\ 0001$) None of the abruptio cases had larger placental infarcts Both the abruptio cases and the controls had only a 2% frequency of necrosis of the decidua basalis at the margin of the placenta None of the umbilical cords in either the abruptio cases or the controls were less than 20 cm

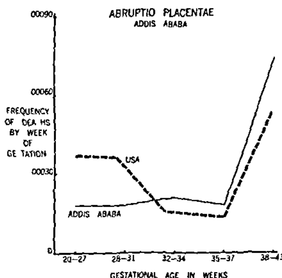


Fig 1 Perinatal deaths due to abruptio placentae had a peak at term in both Addis Ababa and in 12 U S cities (8)

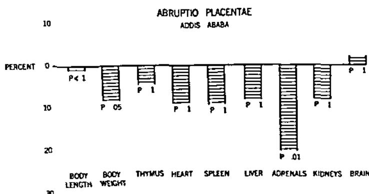


Fig 2 Organ and body measurements from fetuses and neonates who died as a consequence of abruptio placentae significantly deviated from published control values The deviations are in percentages Adrenals livers and thymuses were more affected than brains and most other organs Student s *t* test was used to determine the significance of the deviations

long so none were considered to be abnormally short

The fatalities were strongly associated with extreme poverty and lack of maternal prenatal medical care (Table I) The deaths were more frequent with maternal diastolic blood pressures under 70 mmHg than with higher pressures Blood loss was greater in many of those with the lower pressures The mean height of mothers who had the fatal abruptions was 153 2 cm and the controls 156 2 cm ($P>0\ 1$) The mean body weight of the mothers who had the abruptions was 50 1 kg on the day after delivery and for the controls 51 0 ($P>0\ 1$) Pregnancy weight gain data were not available on enough of the abruption cases to make a meaningful analysis possible

None of the following maternal factors had any significant influence on perinatal death rates due to placental abruptions age cigarette smoking tribe religion rural or urban residence type of facility used for excreta disposal number of sexual partners number of prior pregnancies preterm deliveries and perinatal losses There was also no association of the deaths with the following pregnancy factors specific maternal illnesses including parasitic infections medications used type of work by mother her hemoglobin levels proteinuria peripheral edema and hydramnios The deaths did not relate to the infant s sex presentation at delivery duration of labor or the use of oxytocic or anesthetic agents

DISCUSSION

Abruptio placentae is initiated by hemorrhage into the decidua basalis which then splits leading to separation of the placenta from the uterine wall The traditional explanations for the separations trauma hydramnios short umbilical cords and congenital anomalies will explain none of the fatal abruptions in the present study (3 10 11) In fact such causes explained only a few percent of the fatal abruptions in a recent large U S study (8) About 30% of the U S cases were explained by decidual necrosis at the margin of the placenta and by large placental infarcts lesions not responsible for the Addis Ababa abruptions The only placental abnormality detected in the Ethiopian abruptio cases was an increased frequency of small placental infarcts However they were found in only 12% of cases and such small infarcts are present in about 18% of placentas in successful U S pregnancies (8)

Other findings in the study offer clues to the genesis of the placental abruptions There was a very strong association of the fatal abruptions with severe poverty Gestational undernutrition and malnutrition are common in Addis Ababa particularly in the poor who must spend most of their incomes on food (1) The resultant diets are mark

Table II *Mean grades for histologic maturity (5)*

Fetal lung maturity in the abruptio cases was accelerated at every gestational age by comparison with U S controls (6)

Gestational age (weeks)	U S controls	Addis Ababa abruptio placentae
20–24	2 4±1 1 (105)	3 3±0 7 (9) $P<0\ 01$
25–27	3 8±0 6 (97)	3 9±0 6 (7) $P>0\ 1$
28–32	4 0±1 4 (109)	5 3±0 7 (9) $P<0\ 01$
Over 32	5 8±0 5 (114)	6 0±0 (48) $P<0\ 01$

Number of cases are in parentheses Mean values are are ±1 S D

edly deficient in calories vitamin A and calcium somewhat less deficient in protein and generally adequate in other vitamins including folic acid (1) These nutritional deficiencies were the likely cause of the fetal growth retardation in the abruptio victims The victims had normally grown brains and growth retarded adrenals spleens and livers a pattern characteristic of fetal undernutrition (4) A similar pattern of fetal growth retardation was recently found in U S victims of abruptio placentae (8) The accelerated lung maturation found in the abruptio victims of the present study has been previously reported in undernourished neonates and related to gestational undernutrition in their mothers (5 6) Thus findings in the present study support a previous suggestion that undernutrition or malnutrition of the gravida may predispose to abruptio placentae (8) The placental or uterine mechanisms through which this might be effected are not known

ACKNOLEDGEMENT

Mr J B Dixon performed most of the statistical analyses the study The study was supported by U S Public lth Service Grant HD 08139-0?

REFERENCES

1 Gebre Medhin M & Gobezie A Dietary intake in the third trimester of pregnancy and birth weights of offspring among nonprivileged and privileged women Am J Clin Nutr 28 1322 1975
2 Gruenwald P & Minh H N Evaluation of body and organ weights in prenatal pathology I Normal standards derived from autopsies Am J Clin Pathol 34 ?47 1960
3 Hibbard B M & Jeffcoate T N A Abruptio placentae Obstet Gynecol 27 155 1966
4 Naeye R L & Kelly J A Judgment of fetal age Pediatr Clin North Am 13 849 1966
5 Naeye R L Freeman R K & Blanc W A Nutrition sex and fetal lung maturation Ped Res 8 200 1974
6 Naeye R L Fetal lung and kidney maturation in abnormal pregnancies Arch Pathol 99 533 1975
7 Naeye R L Tafari N Judge D Gilmour D & Marboe C Amniotic fluid infections in an African city J Pediatr 90 865 1977
8 Naeye R L Harkness W L & Utts J Abruptio placentae and perinatal death a prospective study Am J Obstet Gynecol 128 740 1977
9 Naeye R L Tafari N Marboe C C & Judge D M Causes of perinatal mortality in an African city Bull WHO (in press)
10 Page E W King E B & Merrill J A Abruptio placentae Obstet Gynecol 3 385 1954
11 Pritchard J A Mason R Corley M & Singue P Genesis of severe placental abruption Am J Obstet Gynecol 108 22 1970

Submitted for publication March 30 1978

Richard Naeye
Department of Pathology
M S Hershey Medical Center
The Pennsylvania State University
College of Medicine
Hershey Pennsylvania 17033
USA

Acta Obstet Gynecol Scand 58 41–44 1979

NEUROBEHAVIORAL RESPONSE OF INFANTS AFTER PARACERVICAL BLOCK DURING LABOUR

Britt Ingjerd Nesheim Ellen Lindbæk Ingebjørg Storm Mathisen
and Helge Jenssen

Department of Pharmacology University of Oslo Norway Departments of Anesthesiology Pediatrics and Gynecology and Obstetrics Aker Hospital Oslo Norway

Abstract 30 parturient women were randomized into a group receiving paracervical block (PCB) and a control group The infants were tested by a neurobehavioral examination immediately after birth after 3 hours and 3 days The examiner was unaware of the obstetrical management of the patients No clinically significant differences could be detected between the two groups Arterial and venous pO pCO and pH from the umbilical cord showed no differences between the groups

Local regional anesthesia during childbirth has gained wide popularity It is efficient relatively easy to administer and it has been thought to have few serious side effects both for the mother and the infant There have however been reports which have given rise to concern about the consequences for the infant of this type of anesthesia When testing neurobehavioral responses after birth Standley et al (10) found decreased motor maturity and increased irritability in infants whose mothers had received local anesthesia (mostly saddle block) during labour The anesthetics used were lidocaine tetracaine mepivacaine and bupivacaine In a similar investigation Scanlon et al (8) characterized the infants born to mothers who had received epidural block with lidocaine or mepivacaine as floppy but alert These infants scored less well on tests designed to test muscle strength and tone than infants born to mothers who had received low spinal local anesthesia or no anesthesia Later an uncontrolled study (9) has reported normal neurobehavioral responses after epidural block with bupivacaine

Paracervical block (PBC) has been used as a routine in our department for 7 years During the years 1972–75 inclusive 930 patients have received one or two blocks during 1st stage of labour The frequency of bradycardia was 2 9% The frequency of one minute Apgar score 7 points or less was 4 7% compared to 7% in all the patients delivered during the same period Because PCB has been so extensively used we felt that it was of importance to know whether this method could affect the neurobehavioral responses of the infant

MATERIALS AND METHODS

Design of the study

The optimal design of a clinical study is to compare two groups of patients who differ only in the variable one wishes to study When testing obstetrical anesthesia it is not possible to achieve this optimal situation Three different designs are possible

1) The patients select themselves into the test or the control group depending on whether they need anesthesia or not Those needing anesthesia would then receive PCB the others nothing Such self selection might introduce bias into the investigation mothers who need no anesthesia would tend to have easier and shorter labours than those needing pain relief This might affect the infants Furthermore the two groups of women might differ constitutionally thus again affecting the newborn

2) The patients are randomized into two groups one receiving PCB the other receiving nothing Thus no bias would be introduced However with this design the control group would contain patients with extremely painful labours being in need of some form of analgesia The neurobehavioral responses of an infant born after a painful labour might differ from those of an infant born almost without pain Furthermore such a design is ethically unacceptable

3) The patients are randomized into two groups one receiving and one not receiving PCB Additionally both groups get other drugs which give some pain relief to the control group This is a pragmatic design because obstetrical patients in a modern ward will almost always receive some sort of pain relief Performed this way the study will reveal whether PCB will affect the infants when given in addition to the standard regime We decided to use this design

Patients

33 parturients were entered into the study when they came to hospital for an anticipated normal labour either spontaneous or induced with oxytocin All pregnancies

Table I *Study population*

Median ranges in parentheses

	PCB	Control
Number of patients	12	18
Mother s age	27 5 (18–37)	25 5 (18–32)
Parity	1 (1–3)	1 (1–3)
Duration of labour	4 5 h (1 5–6 5)	7 h (1 5–14)
Pregnancy week	41 (39–43)	41 (38–44)
Weight of infant	*3 745 g (2 800–4 230)*	*3 760 g (2 720–4 800)*
Apgar score 1 min	9 (7–9)	9 (6–10)
Apgar score 5 min	9 (9–10	9 (9–10)
Number of labours induced with oxy tocin	4	6

had been uneventful and the women had received routine antenatal care When labour was established and the pa tient thought to be suited to take part in the study she was randomized into one of two groups the PCB group or the control group The randomizing was done by tossing a coin

Drugs

The control group received a somewhat standardized variant of the scheme normally followed for pain relief in the department diazepam 10 mg and/or promazine mg N_2O+O_2 50/50% intermittently and infiltration hesia with lidocaine ½% / adrenaline 1/200 000 10 ml ately before the *episiotomy was made The PCB* group received diazepam 10 mg and/or promazine 25 mg N_2O+O_2 50/50% intermittently For the PCB bupivacaine 1/4% / adrenaline 1/400 000 16 ml was used In our ward PCB is always accompanied by pudendal block with lidocaine ½% / adrenaline 1/200 000 10 ml on each side plus *10 ml perineal infiltration The patients in the control* group thus received 50 mg lidocaine those in the PCB group 150 mg lidocaine and 40 mg bupivacaine

All PCB s were done by the same obstetrician (H J) at approximately 5 cm cervical dilation A modified Kobak needle was used Marcain Adrenalin ½% ® Bofors 10 ml was diluted with 10 ml 0 9% NaCl solution Injection of 4 ml was made at 4 points in the vaginal lateral fornices corresponding to 3 4 30 7 30 and 9 o clock Care was taken to deposit the anesthetic solution as superficially as possible preferably where maximal resistance to injection was found This technique retards absorption (6) and in our experience gives maximal pain relief Fetal puncture was *avoided by a tangential positioning of the needle in* relation to the presenting part (4) and by the technique of Ingelman Sundberg (5) Pudendal block was given by the nurse midwife when the cervix was fully delated

After a patient had been entered into one of the two groups the investigators did not play any part in the obstetrical management which was taken care of by the nurse midwife on duty as customary She was instructed that if she felt that a patient in the control group needed more anesthesia she was free to give it The patient was then removed from the study This happened only once The patients who were randomized into the PCB group were offered PCB in such a way that they were free to refuse if they did not want anesthesia in which case they would have been removed from the study This never happened

Immediately after birth arterial and venous blood sam ples were taken from the umbilical cord for acid/base measurements

The neurobehavioral testing procedure and scoring criteria were identical to those described by Scanlon et al (8) The examination comprises a series of tests evaluating the infant s responses to various stimuli sound light and pin prick his muscular power and tone as well as several reflexes Scores from 0–3 were given for each test In addition the number of stimuli required to give a notice able change of the response was recorded i e the re sponse decrement behaviour

The examination was performed as soon as possible *usually 15 to 30 min after delivery it was repeated after 3* hours and the final examination took place 3 days later

The same pediatrician (I S M) examined all the in fants The examiner was unaware of the delivery course and of the type of anesthesia used The scoring schemes from the neurobehavioral test were kept by the pedia trician and the results were not confided to the other in vestigators before the code was broken at the end of the trial

Apgar score at one and five minutes after birth were determined by the midwife The temperature of the infant was recorded before and after each examination to ensure that hypothermia did not influence the test results

An independent pediatrician was responsible for the routine examination and care of the newborn infants

Of the 33 patients entering the study 3 had to be left out One in the control group who needed more an esthesia 2 in the PCB group one because the pediatri cian was told which group the mother belonged to and one where the PCB was not given for reasons not related to the study The sample thus consisted of 30 infants from 30 mothers of which 12 had received PCB and 18 were controls

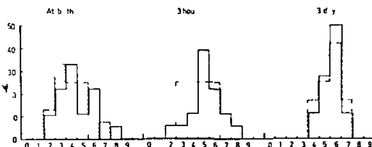


Fig 1 Distribution of the combined scores of 3 tests for muscle tone (pull to sitting arm recoil truncal tone) High scores denote high muscle tone Abscissa. scores Ordinate % of infants Hatched lines PCB group Whole lines control group The infants were tested at birth after 3 hours and after 3 days

RESULTS

Characteristics of the patient population are given in Table I There were no differences between the two groups in any of the characteristics listed in the table except for duration of labour which was significantly shorter in the PCB group ($\alpha=0\ 007$ one sided Wilcoxon two sample test) The mean time between administration of PCB and delivery was 124 min (range 31–280 min)

In the neurobehavioral tests the only differences between the PCB group and control group were in 3 tests for decrement of responses response decrement to pin prick to Moro and to light In each of these tests the PCB group had a somewhat slower response decrement which was clinically small Table II shows the point estimates and 95% confidence limits on the differences between the number of stimuli until change of response in the PCB group and the control group determined by the method described by Noether (7) and interpolated within groups As can be seen from the table the differences were not statistically significant for any of the groups but when the groups were combined and tested with a Wilcoxon van Elteren test statistical significance was reached ($\alpha=0\ 002$)

Fig 1 shows the frequency distributions of the combined scores of 3 tests designed to measure muscle tone pull to sitting arm recoil and truncal tone As can be seen from the figure the scores improved with the age of the infant In the control group combined scores for muscle tone were low (0–4) in 65% and high (5–9) in 35% of the infants immediately after birth whereas the corresponding percentages were 22 and 78 at 3 hours and 11 and 89 at 3 days No differences could be found however between the scores of the PCB group and the control group Neither were any differences found when the 3 tests were considered separately

Likewise no differences could be found between the PCB group and the control group in any other of the tests applied

pH pO_2 and pCO_2 did not differ between the PCB group and the control group

There were however more complicated labours and operative deliveries in the PCB group There were 5 operative interventions in the PCB group and 2 in the control group The difference between the two groups is not statistically significant (Fisher Irwin test two-sided $\alpha=0\ 14$)

DISCUSSION

In the present study detailed neurobehavioral examination of the newborn infant revealed no or only small clinically unimportant effects of local regional anesthesia (paracervical and pudendal block) given to the mothers during childbirth The local anesthesia was given in addition to the drugs normally used during labour in our department diazepam 10 mg and/or promazine 25 mg—mostly only one of the drugs— and N_2O/O_2 intermittently

Table II *Point estimates and 95% confidence limits on differences between decremental responses in PCB and control group*

	Immediately after birth	3 h	3 days
Pin prick	2 0 (−2 5 5 9)	2 3 (−2 ? 7 5)	1 1 (−2 1 4 8)
Moro	? 2 (−0 7 5 5)	1 8 (−1 0 5 5)	0 4 (−2 8 2 4)
Light	0 5 (−1 3 2 1)	1 8 (−1 1 4 2)	1 0 (−1 9 3 1)

The scores on tests of muscle tone immediately after birth and after 3 hours were lower in our study than in those published by other authors (8 9) The scores were improved when the infants were re tested on the third day of life Diazepam in higher doses than those used in this study have been shown to cause hypotonia in the newborn (2 3) 10–15 mg diazepam did not cause hypotonia (2) Nevertheless an effect of diazepam 10 mg or pro mazine 25 mg revealed by this examination must be considered

Previous studies have reported impaired neu robehavioral responses in infants after epidural (8) or local regional (10) anesthesia given during labour In these studies lidocaine tetracaine mepivacaine and bupivacaine were the anesthetics used Normal neurobehavioral responses have been reported after epidural block with bupivacaine (9)

The local anesthetics given to the patients in this study were bupivacaine/adrenaline 40 mg and lidocaine/adrenaline 150 mg in the PCB group and lidocaine/adrenaline 50 mg in the control group No attempt was made in this study to measure plasma [illegible]ion of the local anesthetics Bupivacaine [illegible] well as other local anesthetics must be assumed [illegible] be converted to metabolites which also may have [illegible] anesthetic properties As long as these metabolites cannot be measured plasma concentra tions cannot be expected to be well correlated to the clinical status of the infant

All local anesthetics affect the central nervous system if their concentration is high enough Whether a local anesthetic given to the mother will cause neurological symptoms in the newborn in fant will depend on the amount of anesthetic reach ing the nervous system and the toxicity of the particular drug

Different local anesthetic agents differ in their pharmacokinetical properties The feto/maternal concentration ratios vary the most protein bound drugs having the lowest ratios (1) This seems to be caused by a much lower degree of protein binding in the infant The concentration of free drug in the fetus thus equals that in the mother (11) As the most protein bound drugs also tend to be the most lipid soluble their uptake in fetal tissues will be rather high (1) At the present state of knowledge it is therefore difficult to deduce any degree of fetal toxicity from pharmacokinetic properties Properly conducted clinical studies will be the only way to demonstrate the safety of the use of any procedure using local anesthetic agents during childbirth

It may be concluded that PCB does not affect the newborn infant whether measured by Apgar score or acid/base status A detailed neurobehavioral ex amination did only reveal minimal differences be tween the PCB and the control group

REFERENCES

1 Covino B G & Vassallo H G Local Anesthetics Mechanisms of Action and Clinical Use p 112 Grune & Stratton New York San Fransisco and London 1976
2 Cree J E Meyer J & Hailey D M Diazepam in labour its metabolism and effect on the clinical condi tion and thermogenesis of the newborn *Br Med J 251* 1973
3 Gillberg Chr Floppy infant syndrome and mat ernal diazepam *Lancet 244 1977*
4 Hedberg G Attempts at improving the technique of paracervical anesthesia in labour In Methoden der pharmakologischen Geburtserleichterung und Uterus Relaxation (ed H Jung) p 62 Georg Thieme Verlag Stuttgart 1972
5 Ingelman Sundberg A Praktiska synpunkter på paracervical blockad Lakartidningen *67* 338 1970
6 Jägerholm M Paracervical block in obstetrics An improved injection method Acta Obstet Gynecol *Scand 54 9 1975*
7 Noether G Introduction to Statistics A Fresh Approach p 138 Houghton Mifflin Company Boston 1971
8 Scanlon J W Brown W U Weiss J B & Alper M H Neurobehavioral responses of newborn in fants after maternal epidural anesthesia Anesthesio logy *40* 121 1974
9 Scanlon J W Ostheimer G W Lurie A O Brown W U Weiss J B & Alper M H Neurobehavioral responses and drug concentrations in newborns after maternal epidural anesthesia with bupivacaine Anesthesiology *45* 400 1976
10 Standley K Soule A B Copans S A & Du chowny M S Local regional anesthesia during childbirth Effects on newborn behavior Science *186* 4164 634 1974
11 Thomas J Long G Moore G & Morgan D Plasma protein binding and placental transfer of bupivacaine Clin Pharmacol Ther *19* 476 1976

Submitted for publication Nov 24 1977

Britt Ingjerd Nesheim
Department of Pharmacology
University of Oslo
Blindern Oslo 3 Norway

Acta Obstet Gynecol Scand 58 45–47 1979

BODY WEIGHT IN PAROUS WOMEN IS THERE ANY ALTERATION BETWEEN SUCCESSIVE PREGNANCIES?

J M Beazley and J R Swinhoe[1]

From the Department of Obstetrics and Gynaecology University of Liverpool and the Mill Road Maternity Hospital Liverpool UK

Abstract In 50 women who had five successive pregnancies the difference was studied between the mean maternal weight at the 20th week of gestation and six weeks post partum The difference changed from a weight loss to a weight gain in the fourth and fifth pregnancies The maximum weight increment occurred between the end of the first pregnancy and the 20th week of the second especially in obese multiparae

This paper presents a retrospective analysis of changes noted in the maternal weight of 50 women during five successive pregnancies Owing to present trends in family size and population shift it probably would be impossible to survey a larger group prospectively

Thomson & Hytten (1) showed that 30% of the average weight gained during pregnancy is due to an increase in body fat part of which may be retained after pregnancy Thomson & Billewicz (2) showed that parity adds little to the tendency to increase weight with age and Billewicz & Thomson (3) concluded that parity probably has little influence on the mean weight at successive pregnancies

The present investigation was undertaken to study weight changes throughout the interval during which mothers undertook five successive pregnancies

PATIENTS AND METHODS

A retrospective analysis was undertaken of the case records of all patients between 1965 and 1975 who attended this hospital during five or more consecutive pregnancies During this decade a simple but uniform method was used by the nursing staff to record maternal weights in the antenatal clinic The weighing machines which remained unchanged were serviced regularly

There were 50 women who fulfilled the following criteria in each of their first five pregnancies and were included in this study

1 Maternal weight and height were measured at the 20th week of pregnancy

2 Delivery occurred between 38 and 42 weeks gestation

3 Each mother was weighed six weeks post partum

4 All the pregnancies studied were normal and the infants delivered alive and well

TREATMENT OF RESULTS

Initially it was assumed that the information that would provide the most meaningful index for comparison of differences between pregnancies would be the weight/height ratio of patients

Billewicz Kemsley & Thomson (4) showed that the weight/height ratio is positively correlated with height the Ponderal Index (weight/height×⅓) is negatively correlated with height and the Quatelet s Index (100×weight/height shows little bias and is probably the best index to use

Although the group studied in this survey was small (50) in each of the five pregnancies each patient is acting as her own control It was therefore decided to express alteration between pregnancies as mean weight differences rather than employing Quatelet s Index

RESULTS

In Table I which shows the mean age of the study group in each pregnancy it can be seen that the mean ages range over a decade from 20 76 years (±3 13) to 29 68 years (±4 41) years

In Table II the net gain or loss of maternal weight between the 20th week and the post natal examination in each of the first five successive pregnancies is shown It can be seen there is a progressive increase in maternal weight at the conclusion of

[1] Present appointment Lecturer in Obstetrics and Gynaecology Royal Free Hospital School of Medicine London UK

Table I *Mean age at the 20th week of gestation*

No of pregnancy	Mean age (years)	S D
1	*20 76*	*±3 13*
2	22 66	±7 87
3	24 66	±3 44
4	27 20	±3 91
5	29 68	±4 41

each pregnancy Nevertheless in the first three pregnancies maternal weight at the sixth post partum week is less than at the 20th week of gestation of each pregnancy In the fourth and fifth pregnancies the post partum weight exceeds the weight at the 20th week of gestation of each of these pregnancies In Table III the results for obese patients only are presented A similar pattern of weight changes is evident in each pregnancy though the differences are greater

The difference in mean weight between the post natal visit of one pregnancy and the 20th week of subsequent pregnancy diminished progressively IV)

e weight increment is greatest between the st and second pregnancies in all patients but the maximum weight difference is evident in obese women

DISCUSSION

The mean ages of the patients in this study ranged from 20 76 years (±3 13) in the first pregnancy to 29 68 years (±4 41) in the fifth pregnancy Each

Table II *Mean 20th week (i) and post natal (ii) weight at each gestation*

No of pregnancy	Mean weight (kg)	S D	S E M	Mean weight difference 20th week–post natal
1 (i)	59 01	±9 67	1 37	
1 (ii)	57 54	±9 82	1 38	−1 47
2 (i)	60 17	±10 51	1 49	
2 (ii)	59 13	±10 42	1 47	−1 04
3 (i)	61 30	±11 35	1 60	
3 (ii)	60 65	±11 19	1 58	−0 65
4 (i)	61 69	±12 72	1 73	
4 (ii)	67 67	±12 73	1 80	+0 98
5 (i)	64 70	±13 06	1 85	
5 (ii)	65 20	±13 32	1 88	+1 00

Table III *Mean 20th week (i) and post natal (ii) weights of heaviest quartile at each gestation*

No of pregnancy	Mean weight (kg)	S D	S E M	Mean weight difference *20th week–post natal*
1 (i)	73 02	±7 39	2 13	
1 (ii)	70 53	±8 23	2 37	−2 49
2 (i)	74 84	±8 43	2 43	
2 (ii)	73 54	±8 46	2 44	−1 30
3 (i)	76 88	±9 38	2 71	
3 (ii)	75 53	±9 97	2 86	
4 (i)	78 84	±9 56	2 76	−1 35
4 (ii)	79 43	±10 59	3 06	
5 (i)	80 85	±12 54	3 67	+0 59
5 (ii)	82 43	±12 17	3 51	+1 58

inter pregnancy interval was about two years Age alone is unlikely to have significantly affected weight changes in this group of subjects

A progressive increase in maternal weight was noted at the end of each successive pregnancy However the mean weight lost by the sixth post natal week diminished progressively By the fourth pregnancy the post natal weight exceeded the weight at the 20th week of gestation

In the interval between the end of the first pregnancy and the 20th week of the second maternal weight gain especially in obese multiparae exceeded the increments gained during the intervals between subsequent pregnancies

The findings of this study support the observations of Sheldon (5) and Billewicz & Thomson (3)

ACKNOWLEDGEMENTS

We thank the consultant medical staff of Mill Road Maternity Hospital Liverpool for permission to report

Table IV *Mean inter pregnancy weight difference*

Inter pregnancy signifies the interval between the sixth post partum week and the 20th week of the subsequent pregnancy

Inter pregnancy no	Total group Mean weight difference (kg) post natal–20th week	4th weight quartile Mean weight difference (kg) post natal–20th week
1–2	+2 63	+4 31
2–3	+2 17	+3 34
3–4	+1 04	+3 31
4–5	+1 53	+1 42

patients under their care We also thank Dr P N Asher and Professor B Benjamin for statistical advice

REFERENCES

1 Thomson A M & Hytten F E Proc Nutr Soc *20* 76 1961
2 Thomson A M & Billewicz W Z Proc Nutr Soc *24* xix 1965
3 Billewicz W Z & Thomson A M Br J Prev Soc Med *24* 97 1970
4 Billewicz W Z Kemsley W F F & Thomson A M Br J Prev Soc Med *16* 183 1962
5 Sheldon J H Lancet *2* 97 1949

Submitted for publication Jan 23 1978

J M Beazley
Department of Obstetrics and Gynaecology
University of Liverpool
Liverpool England

Acta Obstet Gynecol Scand 58 49 51 1979

THE PEROXIDASE CONTENT AND THE ANTIBACTERIAL ACTIVITY OF THE AMNIOTIC FLUID

Michael Feingold Samuel Levin and Vaclav Insler

From the Department of Obstetrics and Gynecology Donolo-Zahalon Government Hospital Tel Aviv—Jaffa and Tel Aviv University Sackler Medical School Israel

Abstract A possible relationship between the antibacterial activity of amniotic fluid and its peroxidase content was examined Antibacterial activity assessed by counting colonies of *S aureus* following 24 hour incubation was present in 76 % of the samples studied It was not related to gestational age Peroxidase activity assessed by the 0-dianisidine method was not found in any of the amniotic fluid samples examined

The amniotic fluid (AF) possesses a distinct antibacterial activity against a broad spectrum of bacteria and prevents infection of the amniotic cavity (1 4 5 8 9) It has been claimed that the degree of antibacterial activity of the AF varies with gestational age (GA) between the 19th and the 42nd weeks (8)

The exact mechanism by which AF is able to suppress bacterial growth is yet unknown

In 1974 Larsen *et al* reported the presence of peroxidase in AF (6) Since peroxidase is an ubiquitous enzyme known to exert antibacterial effects in different systems of the body i e saliva leucocytes it seemed conceivable that it might also play a role in he antibaterial activity of the AF (3 7)

The present study was undertaken in order to investigate the presence of peroxidase in AF and if present to determine its relationship to the antibacterial activity of the AF

MATERIAL AND METHODS

Amniotic fluid Sixty six samples of AF were obtained from gravid patients of gestational age between 16 and 42 weeks None of the women included in this study had taken antibiotics during the month preceding amniocentesis None showed clinical signs of infections during or within 24 hours following the procedure

Half the samples were obtained from patients in active labour prior to rupture of the membranes by using a sterile needle inserted through a sterile amnioscope to withdraw about 20 ml of fluid The other half were obtained by aseptic transabdominal amniocentesis Samples containing blood were discarded

Sixty two samples were stored in sterile tubes at 18 C Prior to analysis each sample was centrifuged at 2500 r p m for 10 minutes to remove particulate matter The fluid was then prefiltered and sterilized by Millipore filtration (no 11307 pore size 0.2 μ) Four AF samples were preserved without prefiltration

Assessment of antibacterial activity of amniotic fluid Thirty AF samples were tested for antibacterial activity using *Staphylococcus aureus* (Oxford) The organisms were prepared and the antibacterial activity of the AF samples assessed according to the techniques used by Bergman *et al* (1)

One tenth milliliter of 10^{-4} dilution of an 18 hour culture in trypticase soya broth (TSB) was added to 0 9 ml of AF to give a bacterial concentration at time zero of approximately 10^{4} bacteria per milliliter Bacterial counts were performed at 0 7 and 24 hours by spreading 0 01 ml of the inoculated fluid over the surface of an agar plate Colonies were counted after 24 hours of incubation at 37 C

Peroxidase assay in amniotic fluid Peroxidase activity in 62 AF samples was assayed spectrophotometrically using the method of Maehly and Chance as described in the *Worthington Enzyme Manual* (10) Horseradish peroxidase type II (HRP) was used as a standard throughout the study and assay parameters were developed by adding HRP to water in dilutions of 1 1 1 2 1 4 and 1 8 In addition HRP dilutions of 1 16 and 1 32 were qualitatively examined for peroxidase activity when guaiacol was used as color indicator and compared with results obtained using 0-dianisidine at the same dilutions All observations were made in duplicate

Factors possibly interfering with the detection of peroxidase or diminishing its activity were ruled out by the following procedures

1 To test the effect of storage and filtration of AF on peroxidase activity 2 fresh samples of unfiltered AF (GA 39 weeks and 41 weeks) were examined qualitatively for the presence of peroxidase and the color reaction compared with that of a control test using HRP in water

2 To determine whether peroxidase was present in minute quantities undetectable by the procedure used in the study two samples of AF (GA 38 weeks and 40 weeks) were concentrated 20 times by lyophilization and then examined qualitatively for peroxidase activity again in comparison with a control test using HRP in water

3 To exclude the possibility that peroxidase activity was being inhibited by the presence of some factor in the AF varying dilutions of standard HRP were added to 2 samples of AF (GA 16 weeks and 42 weeks) The results of these assays

Table I *Antibacterial activity in 30 samples of amniotic fluid For each sample the number of colonies per agar plate at 0 and 24 hours of incubation is recorded*

Amniotic fluid sample	No of colonies after incubation time: 0 hour	24 hours
1	71	0
2	205	7
3	50	5
4	39	4
5	50	12
6	161	130
7	159	∞
8	26	13
9	69	9
10	72	∞
11	146	7
12	0	6
13	105	2
14	50	35
15	19	0
16	95	164
17	2	1
18	42	8
19	100	∞
20	24	∞
21	127	∞
22	64	1
23	40	10
24	8	2
25	13	3
26	1	1
[illegible]	5	2
[illegible]	2	0
[illegible]	16	4
[illegible]	8	0
Control	311	∞

were again compared with those obtained when the same dilutions of HRP were added to water

For statistical evaluation of results the Student s t test and the χ (Chi square) distribution were u ed

RESULTS

Antibacterial activity of the amniotic fluid Table I records the antibacterial activity in 30 AF samples expressed as the number of colonies per agar plate at zero time and after incubation for 24 hours in comparison with a control

After incubation for 24 hours antibacterial activity was evident in 76 per cent of AF samples

Correlation of gestational age with degree of antibacterial activity Table II shows the degree of antibacterial activity in the AF of various GA groups expressed as the number of samples showing strong inhibition (<10 colonies) inhibition (10-100 colonies) or no inhibition (>100 colonies) after incubation for 24 hours with *S aureus*

Table II *Degree of antibacterial activity in amniotic fluid samples of various gestational age groups*

	Gestational age in weeks: 16 20	20 28	32 42
Strong inhibition (< 10 colonies)	8	4	8
Inhibition (10—100 colonies)	1	0	2
No inhibition (> 100 colonies)	2	2	3
Total	11	6	13

Statistical evaluation showed that the differences between antibacterial activity of AF samples of various gestational ages were not significant (p > 0 7)

Peroxidase assay In the development of assay parameters by adding varying dilutions of HRP to water peroxidase activity was readily detected in every instance its level being inversely proportional to the dilution of HRP Curves obtained for each dilution showed that interassay differences over a period of 4 days varied by no more than 7 5 per cent In the qualitative tests for peroxidase using two different color indicators no color reaction was seen at dilution greater than 1 16 when guaiacol was used while with 0-dianisidine positive reactions were obtained also at dilution of 1 32

When assaying the peroxidase activity of the 62 AF samples no change in optical density was recorded on the spectrophotometer i e no peroxidase activity was detected in any of the samples

Also peroxidase could not be detected in the 2 samples of fresh unfiltered AF subjected to qualitative analysis or in the 2 samples assayed after lyophilization In each case a control test carried out at the same time using a solution of HRP in water instead of the AF showed a positive result with an orange color developing after 3—4 minutes

Addition of HRP to 2 AF samples produced response curves parallel to the standard curves for each dilution of HRP in water

DISCUSSION

Theoretically infection of the uterine cavity and its contents during pregnancy should be fairly common

This sensitivity to infection stems from the following facts a) The amniotic fluid and decidua provide an excellent culture medium for many types of bacteria b) The female genital organs are known to harbor many micro organisms some of them distinctly pathogenic c) The increased vascularisation of the uterus during pregnancy may enhance the spread of infection should it occur

Despite these extremely favourable preconditions for the occurrence and spread of infection the actual frequency of clinically detectable infection of the uterine cavity is extremely rare

This could be at least partly explained by the antibacterial activity of the AF (1 4 5 8 9) Our study using 30 samples of AF confirms this finding 76 per cent of the samples showing antibacterial activity after incubation for 24 hours These findings are similar to those of Galask and Snyder and of Bergman *et al* (1 2) However we were unable to find a correlation between gestational age from the 19th to the 42nd week and the degree of antibacterial activity of the amniotic fluid This contradicts the findings of Schlivert *et al* based on the study of 22 samples (8) Moreover in our study out of 11 samples prior to the 19th week of gestation 8 showed strong antibacterial activity This is in contrast with Schlivert s finding that antibacterial activity is absent until the 19th week

We were unable to demonstrate peroxidase activity in any of the AF samples assayed The possibility that some peroxidase present might have been destroyed during storage or filtration or that peroxidase was present but in quantities too minute for detection by standard methods was excluded by examination of untreated AF and of untreated fluid concentrated by lyophilization Thus our results do not support the theory that peroxidase acts as an independent antibacterial agent in the AF Furthermore our results contradict those of Larsen *et al* who tested 41 AF samples and found peroxidase activity in 78 per cent of them with an increase in peroxidase level from the 32nd to the 40th week of gestation followed by a decrease towards the 42nd week (6) Guaiacol was used as the color indicator for peroxidase assay in their study however our tests comparing guaiacol and 0-dianisidine as color indicator showed that 0-dianisidine is at least as sensitive an indicator of peroxidase activity as guaiacol

We were able to show that peroxidase activity is not actually inhibited by the presence of some factor in AF as we demonstrated that the curves obtained on adding HRP to AF were similar to those obtained when HRP was added to water

The results of our study indicate that peroxidase plays no part in the antibacterial activity of the amniotic fluid

REFERENCES

1 Bergman N Bercovici B & Sacks T Antibacterial activity of human amniotic fluid Am J Obstet Gynecol *114* 5 0 1972

2 Galask R P & Snyder I S Antimicrobial factors in amniotic fluid Am J Obstet Gynecol *106* 59 1970

3 Klebanoff S J & Lubke R C The antilactobacillus system of saliva Role of salivary peroxidase Proc Soc Exp Biol *118* 483 1965

4 Larsen B Snyder I S & Galas R P Bacterial growth inhibition by amniotic fluid Am J Obstet Gynecol *119* 492 1974

5 Larsen B Snyder I S & Galask R P Bacterial growth inhibition by amniotic fluid Am J Obstet Gynecol *119* 497 1974

6 Larsen B Snyder I S & Galask R P Muramidase and peroxidase activity of human amniotic fluid Am J Obstet Gynecol *44* 219 1974

7 McRiply R J & Sbarra A J Role of the phagocyte in host parasite interaction J Bacteriol *94* 1425 1967

8 Schlivert P Johnson W & Galas R P Bacterial growth inhibition by amniotic fluid Am J Obstet Gynecol *125* 899 1976

9 Schlivert P Johnson W & Galask R P Bacterial growth inhibition by amniotic fluid Am J Obstet Gynecol *125* 906 1976

10 Worthington Enzyme Manual p 43 Worthington Biochemical Corporation Freehold N J 1972

Submitted for publication September 29 1977

Samuel Levin M D
Department of Obstetrics and Gynecology
Donolo-Zahalon Government Hospital
Tel Aviv—Jaffa Israel

Acta Obstet Gynecol Scand 58 53–55 1979

IMPROVEMENT OF DEFECTIVE LACTATION BY USING ORAL METOCLOPRAMIDE

V Guzman G Toscano E S Canales and A Zarate

From the Department of Endocrinology Hospital Gineco Obstetricia No 1 Instituto Mexicano Seguro Social Mexico

Abstract An attempt has been made to pharmacologically enhance PRL secretion to improve lactation Twenty-one puerperal women with past history of defective lactation and PRL levels under the normal range were studied for 4 weeks postpartum Eleven patients who received orally 20 mg a day of metoclopramide showed persistently elevated basal levels of serum PRL during the four weeks observation period These women also had a good milk production and their infants did not need supplements Ten women receiving placebo however showed an abrupt decrease in basal PRL levels and this decrease persisted despite the continuation of lactation Simultaneously a decline in the milk yield was observed and by the 14th postdelivery day milk production was minimal The administration of metoclopramide at this moment to this group of poor lactating mothers produced an increase in serum PRL levels which persisted for the rest of the study Metoclopramide also augmented the milk production so that these women were able to continue breast feeding their infants Our preliminary results seem to prove that defective lactation associated with low prolactin levels (prolactipenia) can be treated by the manipulation of endogenous PRL secretion through the administration of metoclopramide or drugs which enhance PRL release

Several investigators have shown that initiation of milk secretion in the human seems to be closely related to the prolactin release induced by a normal infant s suckling (1–2) Conversely defective lactation has been associated with a defective PRL secretion in response to an impaired suckling (3) On the basis of these observations it has been suggested that milk production might be augmented by the use of pharmacological agents which induce an increase in PRL secretion (4–5) In the present investigation metoclopramide was given to stimulate PRL secretion (6) in puerperal women with a past history of defective lactation Thus the therapeutic effect of metoclopramide was studied

MATERIAL AND METHODS

The study comprised 1 puerperal women para 1–3 who had achieved a full term normal delivery following an uncomplicated pregnancy All the patients had a past history of defective lactation which had necessitated artificial feeding for the infants They were divided into two groups Group "A eleven women received metoclopramide 10 mg capsules twice daily before commencing breast feeding starting within 48 hr of delivery and continuing for 4 weeks Ten patients comprising Group B were given identical capsules containing a placebo In this group those women who reported defective lactation by the second week postpartum were given metoclopramide instead of the placebo for the following two weeks In addition 30 puerperal women with normal lactation were included in the study for comparison Estimations of serum PRL levels were performed weekly on venous blood collected before the first morning breast feeding All serum samples were stored at − 0°C until assayed Milk yield was evaluated by the patient herself as defective moderate and good

Hormone assay

Serum PRL was measured by a modification of the radioimmunoassay described by Hwang et al (7) using human pituitary PRL (hPRL–VLS no 3) Intra and interassay variations were 8 and 10% respectively and the sensitivity of the assays was 2 ng/ml Materials for the radioimmunoassay of PRL were supplied by the Hormone Distribution Program of the NIAMDD by Dr L E Reichert Emory University Atlanta Values in the text and the figures are expressed in ng/ml and given with the standard error The significance of the differences was calculated using the paired Students *t* test values differing from each other at *p*-values of less than 0 05 were considered significant

RESULTS

Fig 1 illustrates the weekly PRL levels in women receiving metoclopramide Immediate postpartum PRL levels were 373 7±34 8 ng/ml which are lower than those observed in normal puerperal women (Table I) Basal PRL levels persisted without significant difference for the subsequent 4 weeks Therefore the gradual decrease in PRL levels which is characteristic of normal lactation was not observed in those women receiving metoclopramide The group treated with placebo had

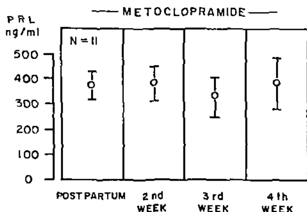


Fig 1 Serum prolactin values of 11 lactating women treated with metoclopramide for 4 weeks

Table I *Serum prolactin concentrations in puerperal women*

MTC=metoclopramide

	Normal lactating women (n=30)	MTC treated group (n=11)	Placebo and MTC treated group (n=10)
First day postpartum	465 ±57 7	373 7±34 8	370 4±46 8
Postpartum weeks			
2nd	234 0±31 4	379 6±51 4	149 8±14 2
3rd	160 0±27 3	338 1±59 2	286 1±45 6
4th	98 [illegible]±17 1	383 4±74 9	180 5±52 8

postpartum basal PRL concentrations similar to those of the metoclopramide treated group however PRL levels showed a significant decrease (p<0 01) to 149 8±14 2 ng/ml by the second week postpartum (Fig 2) At this time metoclopramide was commenced and after one week of treatment the PRL concentrations became elevated to levels similar to those found in the immediate postpartum and remained elevated throughout the All patients treated with metoclopramide in the immediate postpartum period had lactation during the 4 weeks observation period The amount of milk yield was considered as good by the mother as their children needed no supplemental feeding Those women who received the placebo noticed a progressive diminution of milk production however as soon as these patients were given metoclopramide there was an increase in milk yield enough to satisfy the infant s nutritional needs Satisfactory lactation was maintained during the following two weeks

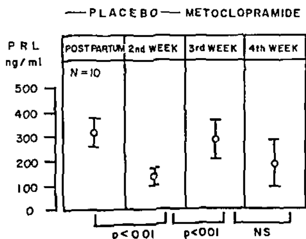


Fig 2 Prolactin concentration in 10 puerperal patients with defective lactation before and after receiving oral metoclopramide

DISCUSSION

It has been assumed that minimal basal PRL concentrations play an important role in the initiation and maintenance of milk secretion likewise it has been suggested that there is no correlation between the basal PRL levels and the amount of milk produced within 4 weeks after delivery (4–5) Aono et al demonstrated that in the early postpartum period milk production correlates well with post suckling PRL release but not with the basal PRL value (3) The present study carried out on mothers with a past history of defective lactation revealed serum PRL levels below the normal range in the immediate postpartum period In these cases a functional disturbance in the hypothalamo pituitary system could have impaired the PRL release which is essential for good lactation The use of metoclopramide in women with defective lactation in the past resulted in an increase in PRL concentrations as well as an improvement in the milk yield In a previous study from our laboratory the oral administration of 60 mg TRH to normal lactating women produced a marked increment in basal PRL concentration and PRL release in response to suckling but no significant augmentation of milk yield was observed (5) The apparent discrepancy could be due to the fact that in cases with full lactation the pharmacological enhancement of PRL secretion has no additive effect on milk production however

in those patients with defective lactation and impaired PRL secretion the administration of drugs which induce PRL secretion may prove useful To conclude the present study showed that lactation may be improved in women with defective lactation who present a certain degree of insufficient PRL secretion In addition the failure to increase PRL release by the use of either TRH or metoclopramide in women with impaired lactation may indicate the presence of a defective mechanism for PRL secretion

ACKNOWLEDGMENTS

This research was supported in part by a Grant awarded by the Academia Nacional de Medicina de México

REFERENCES

1 Ho Yuen B Keye W R & Jaffe R B Human prolactin secretion regulation and pathophysiology Obstet Gynecol Surv *28* 527 1973
2 Noel G L Suh H K & Frantz A G Prolactin release during nursing and breast stimulation in postpartum and nonpostpartum subjects J Clin Endocrinol Metab *38* 413 1974
3 Aono T Shioji T Shoda T & Kurachi K The initiation of human lactation and prolactin response to suckling J Clin Endocrinol Metab *44* 1101 1977
4 Tyson J E Friesen H G & Anderson M S Human lactation and ovarian response to endogenous prolactin release Science 177 897 1972
5 Zárate A Villalobos H Canales E S Soria J Arcovedo F & MacGregor C The effect of oral administration of thyrotropinreleasing hormone on lactation J Clin Endocrinol Metab *43* 301 1976
6 Judd S J Lazarus L & Smithe G Prolactin secretion by metoclopramide in man J Clin Endocrinol Metab *43* 313 1976
7 Hwang P Guyda H & Friesen H A radioimmunoassay for human prolactin Proc Nat Acad Sci (USA) *68* 1902 1971

Submitted for publication Nov 14 1977

A Zárate M D
Department of Endocrinology
G Mancera 2??
Mexico 1– D F
Mexico

Acta Obstet Gynecol Scand 58 57–58 1979

EARLY SUCCESSFUL PREGNANCY FOLLOWING TUBERCULOUS ENDOMETRITIS

Colm O Herlihy

From the Institute of Obstetrics and Gynaecology Hammersmith Hospital London England

Abstract Successful pregnancy following proven endometrial tuberculosis is rare Such a case is reported where conception occurred within three months of finishing treatment It is suggested that rifampin may offer a better prospect of subsequent fertility than other chemotherapeutic agents

Tuberculous endometritis (TBE) has diminished in frequency in the past decade following a general decline in prevalence of tuberculosis It has formerly been associated with a dismal prognosis for further fertility even after prolonged chemotherapy (7) Improvements in culture techniques have recently increased accuracy of diagnosis (6 5) while the introduction of rifampin (rifampicin) as a potent anti tuberculous agent has shortened the duration of therapy (2) and may have enhanced the prospect of fertility following treated genital tuberculosis A patient is reported who conceived only three months after cessation of rifampin chemotherapy for proven TBE and who subsequently delivered a healthy infant

CASE REPORT

A 25 year-old Greek Cypriot immigrant was referred for investigation of primary infertility after almost two years of marriage No personal or familial history of tuberculosis or other serious illness was obtained Physical examination was normal and tubal patency was demonstrated by insufflation Seminal analysis and post coital cervical aspirates confirmed the presence of ample normal spermatozoa Basal body temperature records repeatedly showed biphasic monthly patterns and normal secretory endometrium was present on biopsy However late-cycle endometrial culture on selective Kirchner medium and oleic acid albumin agar slopes with added anti bacterial agents yielded Mycobacterium tuberculosis Chest radiography and urine and sputum examinations and culture were normal

Daily oral therapy with rifampin 450 mg and isoniazid 300 mg was commenced and continued for ten months After cessation of treatment neither culture nor histological examination of the endometrium showed any evidence of tuberculosis Tubal patency was then again conformed by insufflation and the patient conceived three months after chemotherapy was discontinued

The pregnancy progressed normally until the final trimester when mild pre-eclampsia developed in association with persistent breech presentation Elective Caesarean section was performed at 38 weeks gestation and a healthy female infant weighing 2 91 kg was delivered Inspection of the ovaries and Fallopian tubes at operation revealed no abnormality and decidual culture and histology were negative Breast feeding was established and the puerperium was uneventful

DISCUSSION

In Britain TBE now occurs chiefly in recent immigrants from areas where extra genital infection is still common In only fifty per cent is a history of earlier tuberculous infection or contact obtainable (4) Previous sterility is the commonest and often the only symptom at diagnosis Schaefer has estimated that up to five per cent of infertile women suffer from genital tuberculosis and considers exclusion of this treatable disease desirable in every case of primary infertility (8)

Direct endometrial culture on selective media with added antibacterial agents has supplanted guinea pig inoculation and Lowenstein Jensen slopes as the most effective diagnostic method (6 5) Such culture is also more likely to detect the disease than endometrial histological examination (4) although several attempts at isolation are justified when other clinical features are suggestive of tuberculosis Rifampin has largely replaced streptomycin as the most potent anti tuberculous bactericidal agent and is usually combined with isoniazid It has the advantages of oral administration for shorter periods Relapses are less common and toxicity less frequent and serious although menstrual disturbance may occur (1)

Tubal patency can be demonstrated in half the

cases of TBE (3) but tubal and endometrial damage usually prevents conception even following prolonged chemotherapy When pregnancies have occurred the majority have ended in abortion or ectopic gestation At best only two per cent of patients have carried to term (4) and some authors have virtually discounted the possibility of a successful outcome (9)

In the case reported one year's treatment was planned but the patient discontinued her drugs after ten months and conceived three months later The early diagnosis of TBE before development of endometrial histological change had an important influence on subsequent conception However the prompt response suggests that rifampin may offer an improved outlook for fertility in genital tuberculosis when the Fallopian tubes are still patent

ACKNOWLEDGEMENT

I am grateful to Professor J C McClure Browne for his helpful advice and for permission to publish this case

REFERENCES

Altschuler S L & Valenteen J W Amenorrhoea following rifampin administration during oral contraceptive use Obstet Gynecol *44* 771–772 1974
2 East African-British Medical Research Councils Controlled clinical trial of four short course regimens of chemotherapy for treatment of pulmonary tuberculosis Lancet *2* 237–240 1974
3 Francis W J Female genital tuberculosis A review of 135 cases J Obstet Gynaec Br Commonw *71* 418–428 1964
4 Jeffcoate T N A Principles of Gynaecology 4th ed pp 296–301 Butterworth London 1975
5 Marks J Ending the routine guinea pig test Tubercle *53* 31–36 1972
6 Mitchison D Allen B & Lambert B Selective media in the isolation of tubercle bacilli from tissues J Clin Path *26* 250–252 1973
7 Schaefer G Full term pregnancy following genital tuberculosis Obstet Gynecol Surv *19* 81–96 1964
8 Schaefer G Female genital tuberculosis Clin Obstet Gynecol *19* 223–239 1976
9 Ylinen O Genital tuberculosis in women Acta Obstet Gynecol Scand Suppl 60 2–34 1961

Submitted for publication October 28 1977

Colm O Herlihy
Department of Obstetrics
and Gynecology
University of Melbourne
Parkville
Victoria
Australia 3052

Acta Obstet Gynecol Scand 58 59–64 1979

DIAGNOSTIC EVALUATION OF PROGESTERONE

Challenge Test in Amenorrheic Patients

Ryosuke Nakano Nobuyuki Hashiba Motoo Washio and Shimpei Tojo

From the Department of Obstetrics and Gynecology Kobe University School of Medicine Kobe Hyogo 650 Japan

Abstract Forty-one amenorrheic patients were grouped on the basis of presence or absence of withdrawal uterine bleeding *following the intramuscular administration of* progesterone Ovarian volume ovarian morphology with particular reference to presence or absence of follicles and state of follicular development and steroidogenic function were investigated in each group Most of amenorrheic patients with progesterone induced uterine bleeding had relatively large ovaries with follicles of high developmental stage (tertiary—Graafian follicle) and responded to exogenously administered HMG and HCG with a rise in the 24-hour urinary excretion of total estrogens In contrast most of amenorrheic patients without progesterone induced uterine bleeding had relatively small ovaries without follicles or with follicles of low developmental stage (primordial—secondary follicle) and did not respond to exogenous HMG and HCG The results of the present study suggest that presence or absence of progesterone induced uterine bleeding is closely correlated with the volume morphology and steroidogenic function of the ovary in amenorrheic patients Thus pathologic amenorrhea could be divided into two groups by utilizing the progesterone challenge test and this clinical categorization might be useful for the diagnosis and treatment of amenorrheic patients

Amenorrhea failure to menstruate is a symtom rather than a disease and has many possible causes Pathologic amenorrhea can result from disturbed function anywhere in the hypothalamic pituitary ovarian uterine axis with or without and an associated organic lesion Pathologic amenorrhea is usually categorized as primary when menarche has never occurred or secondary when a previously established menstruation ceases In Germany amenorrhea is categorized from another point of view as Amenorrhoe 1 Grades or Amenorrhoe 2 Grades by utilizing presence or absence of withdrawal uterine bleeding following the intramuscular administration of progesterone (10) This clinical categorization has proved useful the diagnosis and treatment of primary and secondary amenorrhea (6 7 9)

The present paper relates the presence or absence of progesterone induced uterine bleeding to the morphology and steroidogenic function of the ovary in amenorrheic patients

MATERIALS AND METHODS

Forty-one amenorrheic patients were investigated Twenty patients had primary amenorrhea and twenty-one patients had secondary amenorrhea An injection of progesterone (25 mg) was first given intramuscularly to each amenorrheic patient Patients who did not respond to this

Table I *Distribution of patients with primary and secondary amenorrhea with and without progesterone induced uterine bleeding according to their probable diagnosis*

Primary amenorrhea	
Progesterone challenge test positive	
Unknown etiology	3
Progesterone challenge test negative	
Turner s syndrome	4
Gonadal dysgenesis with normal karyotype	6
Primary ovarian failure (Atrophic or hypoplastic ovary)	5
Unknown etiology	2
Total	~0
Secondary amenorrhea	
Progesterone challenge test positive	
Polycystic ovary syndrome	5
Premature menopause	1
Unknown etiology	5
Progesterone challenge test negative	
Premature menopause	4
Pituitary adenoma	2
Sheehan s syndrome	1
Forbes Albright s syndrome	1
Unknown etiology	2
Total	21

Table II *Correlation of progesterone challenge test and ovarian morphology especially presence or absence and developmental stage of follicles in patients with primary and secondary amenorrhea*

	Amenorrhea		Ovarian follicle		
				Presence Developmental stage	
	Primary	Secondary	Absence	Low	High
Progesterone challenge test positive	3	11	0	1	13
Progesterone challenge test negative	17	10	10	10	7
Total	20	21	10	11	20

test dose of progesterone were given an increased dose of progesterone (50 mg) intramuscularly Thus the amenorrheic patients were grouped on the basis of presence or absence of withdrawal uterine bleeding following the intramuscular injection of progesterone

The distribution of patients with primary and secondary amenorrhea with or without progestrone induced uterine bleeding according to their probable diagnosis is shown in Table I

Ovarian biopsy was performed in the amenorrheic patients Specimens were fixed sectioned and stained with ylin and eosin and examined microscopically for or absence of ovarian follicles The cases with follicles were further grouped on the basis of the developmental stage of the follicles cases with follicles of low developmental stage (primordial—secondary follicle) and of high developmental stage (tertiary—Graafian follicle) For histochemical study the ovarian tissue was *quickly frozen on dry ice stored at −15 C Sections of the* frozen tissue were cut at 14 μ in a cryostat and picked up on a coverslip They were allowed to dry at room temperature for about 10 min The incubation conditions used to demonstrate glucose-6-phosphate dehydrogenase (G-6-PD) (8) and Δ^5 3β hydroxysteroid dehydrogenase (3β HSD) (17) have been described elsewhere

Urinary excretion of total estrogens in *normal ovulating*



Fig 1 Histochemically demonstrated G-6-PD in theca interna *of a growing follicle in an amenorrheic patient with* progesterone induced uterine bleeding (×140)



Fig 2 Histochemically demonstrated 3β HSD in luteinized theca interna in an amenorrheic patient with progesterone induced uterine bleeding (×28)

females and amenorrheic patients was measured in ?4 hour samples according to the method of Brown et al (?) Exogenous gonadotropins human menopausal gonadotropin (HMG) and human chorionic gonadotropin (HCG) were administered to *normal ovulating women* and amenorrheic patients and the ovarian response was evaluated by daily estimation of the ?4 hour urinary excretion of total estrogens The HMG used was Humegon (Organon Amsterdam The Netherlands) Each ampule contained 75 IU (2nd IRP–HMG) of FSH activity and ?4 IU (?nd IRP–HMG) of LH activity The HCG used was Gonatropin (Teikoku Hormone Tokyo) and its activity was calibrated against ?nd IS–HCG HMG (150 IU) and HCG (3 000 IU) were administered by intramuscular injection on the 1st and the 3rd days of the schedule Total urinary estrogens were measured in ?4 hour samples for 5 consecutive days

Relationships between ovarian volume and urinary estrogens in amenorrheic patients were studied For calculation of ovarian volume the ovary has been assumed to be an ellipsoid and the standard formula $V = \frac{1}{6}abc$ has been used where a b and c are the principal diameters of the ovary (1) The combined volume of both ovaries was used in this study

Eleven normal ovulating females with uterine myoma whose ages ranged from 24 to 30 years served as controls All the women had regular ovulatory menstrual cycles with intervals between periods from ?8 to 3? days *Urinary excretion of total estrogens and estrogen response to exogenously administered gonadotropins were studied in these subjects during the follicular phase of the menstruation cycle (cycle day 7) The ovarian volume was determined when abdominal myomectomy or hysterectomy was performed*

Informed consent was obtained from each subject after full explanations of the purpose and nature of this study

RESULTS

Three of the twenty patients with primary amenorrhea and eleven of the twenty one patients with secondary amenorrhea responded to intramuscular injection of progesterone with withdrawal uterine bleeding All the fourteen amenorrheic patients responding to the progesterone challenge test with bleeding had follicles in their ovaries thirteen of them had follicles of high developmental stage (tertiary—Graafian follicle) and only one of them had follicle of low developmental stage (primordial—secondary follicle) In contrast ten of the twenty seven patients who did not respond to the progesterone challenge test had no ovarian follicles and seventeen of them had follicles of various developmental stages Seven of the seventeen patients had follicles of high developmental stage and ten of them had follicles of low developmental stage (Table II)

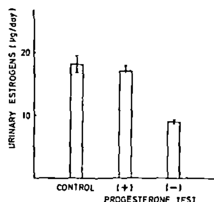


Fig 3 The 24 hour urinary excretion of total estrogens in normal control subjects and amenorrheic patients with positive and negative progesterone induced uterine bleeding

Glucose 6-phosphate dehydrogenase (β 6-PD) and Δ^5 3β hydroxysteroid dehydrogenase ($3\approx$ HSD) were demonstrated histochemically in foci in the internal theca layer of growing follicles (Fig 1) the luteinized theca layer (Fig 2) in stromal hyperthecosis the corpus fibrosum and corpus luteum These enzymes were abundantly demonstrated in the ovary of amenorrheic patients with progestrone induced uterine bleeding On the contrary the enzyme activities were scanty or lacking

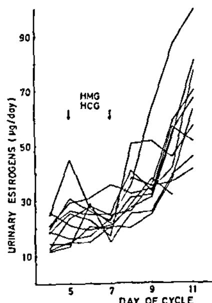


Fig 4 The ovarian response to exogenously administered HMG and HCG on cycle day 5 and 7 in normal ovulating women in the follicular phase of the menstrual cycle

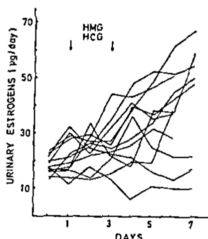


Fig 5 The ovarian response to exogenously administe HMG and HCG on days 1 and 3 of the gonadotro challenge test in amenorrheic patients with posit progesterone induced uterine bleeding

in the ovary of amenorrheic patients witho progesterone induced bleeding

The 24 hour urinary excretion of total estroge in amenorrheic patients responding to the pr gesterone challenge test was similar to that seen normal ovulating women in the follicular phase the menstrual cycle Urinary total estrogens in p tients without progesterone induced uterine blee ing were lower than those in normal control su jects ($P<0.05$) (Fig 3)

The ovarian response to exogenous HMG a

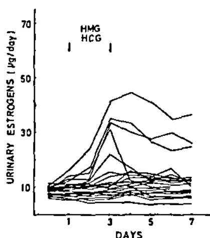


Fig 6 The ovarian response to exogenously administere HMG and HCG on day 1 and 3 of the gonadotropin cha lenge test in amenorrheic patients with negativ progesterone induced uterine bleeding

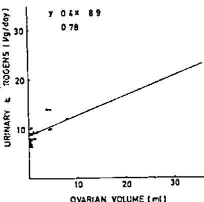


Fig 7 Correlation of ovarian volume and the 24 hour urinary excretion of total estrogens in amenorrheic patients

HCG in normal ovulating women in the follicular phase of the cycle was demonstrated in Fig 4 All the volunteers responded to HMG and HCG with a rise in the 24 hour urinary excretion of total estrogens All of the amenorrheic patients responding to the progesterone challenge test were responsive to exogenous HMG and HCG with an elevation in urinary estrogens (Fig 5) In contrast most of the patients who failed to respond to the progesterone challenge test were not responsive to HMG and HCG (Fig 6)

The volume of the ovaries was closely correlated to urinary excretion of total estrogens in the 24 hour samples in patients with primary and secondary amenorrhea ($r=0.78$) (Fig 7) Ovarian volume in amenorrheic patients with positive progesterone induced uterine bleeding was larger ($P<0.05$) and that in patients with negative progesterone induced bleeding was smaller ($P<0.05$) than that in normal control subjects (Fig 8)

DISCUSSION

It has been reported by a German author (10) that withdrawal uterine bleeding following an intramuscular injection of progesterone has made it possible to divide amenorrhea into two categories Amenorrhoe 1 Grades and Amenorrhoe 2 Grades Progesterone induced uterine bleeding indicates that (i) The endometrium is capable of functioning (ii) Growing follicles exist in the ovary and endogenous estrogenic activity is present as the progesterone can act only on an endometrium adequately primed with estrogen (iii) The anterior pituitary must be providing FSH and LH These conclusions imply that the amenorrheic patient s hypothalamic pituitary ovarian uterine axis is at least relatively intact and that the cause is usually hypothalamic dysfunction (9) Moreover it is reported that most patients responding to a progesterone challenge test are capable of having ovulation induced with clomiphene citrate (6)

Clinical studies of progesterone challenge tests in patients with amenorrhea have been reported by several investigators and its diagnostic value is becoming established (6 7 9 10) However little is known about ovarian morphology especially the state of follicular growth and steroidogenic function in amenorrheic patients investigated in this manner In the present study the relationship between the presence or absence of progesterone induced uterine bleeding and the morphology and steroidogenic function of the ovary in patients with primary and secondary amenorrhea was investigated All of the amenorrheic patients responding to progesterone challenge test had ovarian follicles in their ovaries and most of them had follicles of high developmental stage (tertiary—Graafian follicle) In contrast many of the amenorrheic patients who did not respond to progesterone test had no ovarian follicles or follicles of low developmental stage (primordial—secondary follicle) in their ovaries Histochemically demonstrated steroidogenic foci were also abundant in the ovary of amenorrheic patient with progesterone induced uterine bleeding and scanty or lacking in the ovary of patients without progesterone induced bleeding Thus the result of progesterone challenge test was closely corre

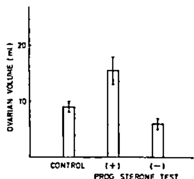


Fig 8 Ovarian volume in normal control subjects and amenorrheic patients with positive and negative progesterone induced uterine bleeding

lated with histological and histochemical findings of the ovary in amenorrheic patients and would be useful for the diagnosis and treatment of amenorrhea

The ovarian response to exogenous gonadotropins in amenorrheic patients has been reported by several investigators (3 4 5 7 9 10 11) In the present study the 24 hour urinary excretion of total estrogens was moderate The ovary responded to exogenously administered gonadotropins by an increase in urinary estrogens in amenorrheic patients who had progesterone induced uterine bleeding In contrast the urinary excretion of estrogens was low and an ovarian response to exogenous gonadotropins could not be demonstrated in most amenorrheic patients with no progesterone induced uterine bleeding The results of the progesterone challenge tests correlated with those of the gonadotropin challenge tests

Although estimation of ovarian size has been reported with particular reference to Stein Leventhal syndrome (1) little information is available about the size and function of the ovary The volume of the ovaries and the 24 hour urinary excretion of total estrogens were closely correlated in this study Ovarian volume was large in amenorrheic patients with progesterone induced uterine bleeding five of whom had polycystic ovary syndrom However ovarian volume was small in patients without progesterone induced uterine bleeding The results suggest that ovarian volume is one of the functional parameters of the ovary

The results of the present investigation indicate that a positive or negative response to progesterone challenge test is closely correlated with the volume morphology and function of the ovary in patients with primary and secondary amenorrhea The progesterone challenge test is of value in the routine investigation of amenorrhea

REFERENCES

1 Abrahams O L Hawkins D F & Lawrence D M Estimation of ovarian size with reference to Stein Leventhal syndrome Obstet Gynecol 38 11 1971
2 Brown J B MacLeod S C Manaughtan C Smith M A & Smyth B A rapid method for estimating oestrogens in urine using a semi automatic extractor J Endocrinol 42 5 1968
3 Cox R I Cox L W & Black T L Test for ovarian function and responsiveness leading to ovulation induction Lancet 2 888 1966
4 Crooke A C Butt W R & Bertrand P V Treatment of idiopathic secondary amenorrhea with single injections of follicle stimulating hormone and human chorionic gonadotropin Lancet 2 514 1966
5 Crooke A C Butt W R & Bertrand P V Clinical trial of human gonadotropins III Variation in sensitivity between patients and standardisation of treatment Acta Endocrinol (Suppl 111) (Kbh) 53 1966
6 Kletzky O A Davajan V & Nakamura R M Thorneycroft I H Mishell D R Clinical categorization of patients with secondary amenorrhea using progesterone induced uterine bleeding and measurement of serum gonadotropin levels Am J Obstet Gynecol 121 695 1975
7 Kupperman H S & Lefkovics S C Progesterone in problem of sterility diagnostic and therapeutic use Fertil Steril 8 131 1957
8 Nachlas M M Walker D G & Seligman A M The histochemical localization of triphosphopyridine nucleotide diaphorase J Biophys Biochem Cytol 4 467 1958
9 Nakano R Hashiba N Kotsuji F & Tojo S A schematic approach to the work up of amenorrhea Fertil Steril 28 229 1977
10 Schrank P Über einen in der allgemeinpraxis anwendbaren Amenorrhoetest Zentralbl Gynakol 74 1569 1952
11 Washio M Fundamental and clinicopathological studies on human gonadotropin action on anovulatory diseases II Studies on the clinical results of artificial induction of ovulation with human gonadotropins and a new trial classification of anovulatory ovaries Kobe J Med Sci 18 41 1972
12 Wattenberg L W Microscopic histochemical demonstration of steroid 3β ol dehydrogenase in tissue sections J Histochem Cytochem 6 225 1958

Submitted for publication Aug 3 1977

Ryosuke Nakano M D
Department of Obstetrics and Gynecology
Wakayama Medical College
1 Shichibancho Wakayama 640
Japan

Acta Obstet Gynecol Scand 58 65–68 1979

EMOTIONAL DISTRESS IN MORNING AFTER PILL PATIENTS

George R Huggins David L Rosenfeld Karl Rickels
Celso-Ramón Garcia and Ellen L Fisher

*From the Department of Obstetrics & Gynecology and of Psychiatry
University of Pennsylvania Philadelphia Pennsylvania USA*

Abstract The self administered SCL 90 test was utilized to collect emotional distress data on 120 female patients requesting morning after pill pregnancy interception SCL prescores were significant in anxiety guilt and depression factors The 2 week post treatment results showed a significant decrease in these factors This test provides reliable measurement of emotional distress factors in gynecologic GYN patients The results must be considered supportive for the use of DES interceptive therapy in spite of other clinical considerations relative to its safety

Since 1966 when Morris & Van Wagenen first described the interceptive action of post coital estrogens in humans (1) numerous studies have documented the effectiveness of this method in preventing pregnancy (2–6) As other clinical aspects of the treatment have yet to be adequately investigated a study was undertaken to explore medical social and emotional factors in morning after pill patients The present report examines the emotional concomitants of morning after pill usage

METHODS AND MATERIALS

Included in the study were 120 patients from the Philadelphia area requesting post-coital contraception during a one year period (October 1973 to October 1974) All patients were seen in the Family Planning Service unit of the Hospital of the University of Pennsylvania As described in greater detail elsewhere (7) each patient was first seen by a Family Planning counselor who obtained a complete demographic and medical history discussed the need for post-coital contraception and explained the potential risks of treatment A technician collected blood samples for several laboratory tests including plasma progesterone and the patient completed an emotional distress checklist (SCL-90) A physician then reviewed the patient s medical history and performed a complete physical examination Patients were given diethylstilbestrol 25 mg to be taken twice daily for 5 days and asked to return to the clinic in 2 weeks for follow up evaluation At the 2 week visit *patients were again interviewed by the Family* Planning counselor and completed a second SCL 90

The SCL 90 is a self report inventory of common psychoneurotic complaints developed by Derogatis et al (8 9) and representing a 90-item version of the Hopkins Symptom Checklist (HSCL) The HSCL has been demonstrated to provide reliable assessment of emotional symptomatology in neurotic patient samples (10) More recently several studies have shown the HSCL to be a useful tool for measuring emotional distress in various obstetric and gynecologic samples (11) The SCL 90 incorporates the five empirically established and validated HSCL factors used in many previous studies (10 11) i e Somatization Obsessive-Compulsive (Performance Difficulty) Interpersonal Sensitivity Depression and Anxiety as well as four new dimensions (8 9) viz Hostility Phobic Anxiety Paranoid Ideation and Psychoticism The SCL 90 also used a 5-point scale (range 0–4) rather than the 4 point scale (range 1–4) of earlier HSCL versions To compare present data with data from previous studies 5 point scores may be converted to 4 point scores Multiply the 5-point score by 0 75 and add 1 0

The 9 SCL 90 factors are derived according to the unit *weight procedure* The patient rates each item on a 5 point scale ranging from not at all [0] to extremely [4] Ratings on all items comprising a given factor are summed and this sum is divided by the number of items rated for that factor Mean factor scores thus range from "0" to 4 with higher scores indicating greater emotional distress Additional SCL 90 measures used as outcome *criteria were the Guilt item (i e feelings of guilt) and* Grand Severity Index (GSI) The GSI is a total score derived by adding the scores of all items rated and then dividing by the number of items rated

While focusing primarily on SCL assessed emotional distress data the present report also considers counselor rated symptom data At both the initial and 2 week visit the Family Planning counselor recorded whether or not the patient experienced each of 23 symptoms These counselor rated symptoms included commonly reported side effects of the present diethylstilbestrol treatment (e g nausea vomiting) many other primarily somatic complaints which might occur as side effects (e g sleepiness mastalgia) and two emotional symptoms (i e anxiety/depression nervousness)

Celso-Ramón García M D 106 Dulles Building 3400 *Spruce Street Philadelphia Pa 19104 USA*

Table I *Emotional distress in morning after pill patients and other family planning service patients*

Hopkins Symptom Checklist (SCL 90)	Morning after pill patients (N=120)		Family planning service patients (N=193)		F ratios
	Mean	S D	Mean	S D	df1 311
Factors					
1 Somatization	0 29	0 37	0 50	0 50	15 51**
2 Obsessive–Compulsive	0 50	0 55	0 53	0 47	0 31
3 Interpersonal sensitivity	0 54	0 59	0 50	0 52	0 24
4 Depression	0 65	0 69	0 66	0 55	0 04
5 Anxiety	0 65	0 60	0 45	0 46	11 10 *
6 Hostility	0 39	0 59	0 57	0 62	6 12*
7 Phobic anxiety	0 26	0 47	0 23	0 37	0 49
8 Paranoid ideation	0 47	0 60	0 56	0 60	1 92
9 Psychoticism	0 29	0 40	0 30	0 40	0 13
Guilt item	0 73	1 06	0 34	0 68	15 60*
GSI (total score)	0 47	0 45	0 50	0 39	0 39

* $p<0.025$ ** $p<0.005$

RESULTS

Several previously reported study findings (7) are briefly noted here in order to provide a context for the emotional distress data to follow

First the 120 morning after pill patients were considerably more socially advantaged than most patients routinely seen in the same Family Planning Service (FPS) unit Data obtained from a survey sample of 193 FPS patients seen for miscellaneous reasons during a specified time period in 1974 may be considered representative Within this FPS sample fully 63% of patients belonged to the lowest social class (class 5) and only 5% were in the highest social classes (classes 1 and 2) 20% were either attending college or had college degrees and 18% were white Within the morning after pill sample only 12% belonged to the lowest social class (class 5) and 35% were in the highest social classes (classes 1 and 2) 62% were either attending college or were college graduates and 88% were white Similar to most other FPS patients most morning after pill patients were young (mean age 21 8) and single (86%)

The majority of morning after pill patients were clearly at risk Specifically 63% of patients reported that sexual exposure had occurred between day 10 and day 18 of their menstrual cycle and 68% of patients were found to have plasma progesterone levels at or below 2 ng/ml

At 2 weeks most patients reported experiencing a variety of somatic side effects with diethylstilbestrol In 24% of patients nausea and vomiting were severe enough to require the use of antiemetics Treatment failure (pregnancy) occurred in 3 patients All 3 had multiple sexual exposure during the treatment cycle and were given therapeutic abortions

Presenting Emotional Distress in Morning After Pill Patients

Table I gives mean prescores and standard deviations for the 9 SCL 90 factors Guilt item and total score (GSI) The scores for the 120 morning after pill patients may be compared with those for the 193 Family Planning Service (FPS) patients described earlier It should be noted that patients in both of these obstetric–gynecologic samples were far less emotionally distressed than typical neurotic patients For example the total scores shown in Table I for morning after pill patients (0 47) and FPS patients (0 50) do not even approach the total score for a representative sample of 577 neurotic females (1 35) (12)

Table I shows that morning after pill patients scored significantly higher than other FPS patients in the Anxiety factor and Guilt item As morning after pill patients were sufficiently concerned about the possibility of an unwanted pregnancy to seek emergency treatment their slightly elevated scores on these two measures make clinical sense Despite their greater situational stress morning after pill patients were similar to routinely seen FPS patients in most other measures and significantly lower than FPS patients in both the Somatization and Hostility factors

Table II *SCL 90 measures showing significant change in patients given the morning after pill (N=102)*

SCL 90 measures	Initial visit		2 week visit		Student s t test
	Mean	S D	Mean	S D	
Somatization factor	0 27	0 35	0 37	0 36	2 35
Anxiety factor	0 6[illegible]	0 55	0 51	0 60	[illegible] 21
Guilt item	0 67	0 99	0 47	0 9[illegible]	[illegible]8

$p<0\ 05$

It was hypothesized that differences between the two samples in somatization and hostility were largely a function of social class whereas differences in anxiety and guilt were not An analysis comparing SCL 90 scores for 95 morning after pill patients and 95 FPS patients matched for social class supported this hypothesis In order to achieve matched samples it was necessary however to omit from analysis 25 morning after pill patients from the highest social classes Specifically the Somatization factor difference became smaller ($F=5\ 53$ $p<0\ 05$) and the Hostility factor difference disappeared ($F=0\ 02$ n s) In contrast morning after pill patients remained far more symptomatic than FPS patients in both the Anxiety factor ($F=17\ 75$ $p<0\ 005$) and Guilt item ($F=15\ 18$ $p<0\ 005$)

While the mean scores for morning after pill patients show a relatively low level of overall emotional distress the standard deviations for the sample are high enough to suggest that some patients were relatively high in emotional symptomatology Previous research (11) has indicated that patients with scores above 1 00 in such clinically relevant factors as Anxiety and Depression could be considered to have emotional distress within a pathological range A total of 38 morning after pill patients (32%) were found to have Anxiety or Depression factor scores above 1 00 Indeed within this subgroup mean scores for the Anxiety (1 28) and Depression (1 40) factors were similar to those observed in neurotic samples

Two Week change in Emotional Distress

A total of 107 patients (89%) returned for their 2 week follow up visit SCL 90 data are available for 102 of these patients Table II gives initial and 2 week data expressed as means and standard deviations for the 3 SCL 90 measures in which Student s t tests showed significant ($p<0\ 05$) change

The significant increase in the Somatization factor is consistent with the reporting of many largely medication related side effects at 2 weeks Indeed t tests conducted for the 23 counselor rated symptoms showed significant increases in a majority of the somatic complaints assessed Increases from the initial to the 2 week period were particularly marked ($p<0\ 001$) for nausea (from 5% to 69%) mastalgia (from 4% to 33%) sleepiness (from 6% to 35%) vomiting (from 2% to 30%) weakness (from 5% to 22%) and edema (from 3% to 19%) Some of these symptoms may have been reported because most patients were seen for their 2 week visit either close to or during their menses

The significant decreases found in the Anxiety factor and Guilt item probably reflect the relief which many patients felt after undergoing treatment to insure against an unwanted pregnancy In addition the Anxiety factor and Guilt item were the two SCL measures in which morning after pill patients initially reported elevated scores and could thus be expected to return to more normal levels In support of these SCL data the counselor rated symptom of nervousness which may be seen as reflecting anxiety also showed significant ($p<0\ 05$) decrease (from 38% to 25%) at 2 weeks

Similar to the total sample the subsample of morning after pill patients with initially high scores (above 1 00) in anxiety or depression reported reduction in emotional distress following teatment In fact t tests conducted for those 30 highly anxious or depressed patients with 2 week data showed a marked ($p<0\ 01$) decrease in the Anxiety factor Patients within this subsample also reported greater reduction in the counselor rated symptoms of nervousness (from 56% to 28%) than was observed for the total sample

CONCLUSION

The SCL 90 was used to collect emotional distress data from 120 primarily young single socially advantaged white females participating in a preg

nancy interception study Patients completed the SCL when they first came to the Family Planning Service (FPS) unit seeking emergency post coital contraceptive treatment and again 2 weeks following onset of treatment with diethylstilbestrol

SCL prescores showed a relatively low level of overall emotional distress for the total sample Compared with a group of FPS patients seen for routine visits morning after pill patients scored significantly higher only in the SCL Anxiety factor and Guilt item At the same time a subsample of morning after pill patients (32%) was found to have SCL Anxiety or Depression factor scores within the neurotic range

Two week SCL data showed significant reduction in the Anxiety factor and Guilt item Significant increase in the Somatization factor reflecting the reporting of many somatic side effects with diethylstilbestrol was also observed Reduction in anxiety was particularly marked for the subsample of patients who were relatively high in initial anxiety or depression Independent symptom ratings made by a Family Planning counselor supported these 2 week SCL findings

It is of interest that the SCL 90 proved sensitive only in reflecting change in emotional distress also in detecting presence of somatic side effects Like previous clinical studies (11) the present study shows the SCL 90 to be a valuable instrument for obtaining reliable information about the impact of obstetric–gynecologic treatment

The major conclusion of these emotional distress data is that patients experienced no negative psychological effects from post coital contraceptive treatment with diethylstilbestrol Indeed despite a drug related increase in somatic complaints most patients reported a decrease in both anxiety and guilt following pregnancy interception These factors must be considered supportive of the use of this agent for interceptive therapy in spite of the other clinical considerations relative to its safety

ACKNOWLEDGEMENTS

This work was supported by USPHS Research Grants MH-08957 and MH-08958 The authors acknowledge with gratitude the scoring of the SCL 90 by Dr Leonard Derogatis of the Hopkins Medical School The assistance of Molly Love Marge Casey Ann Marie Jusczyk and Janice Vlahovich is also gratefully acknowledged

REFERENCES

1 Morris J M & Van Wagenen G Compounds interfering with ovum implantation and development Am J Obstet Gynecol 96 804 1966
2 Morris J M & Van Wagenen G Interception The use of post ovulatory estrogens to prevent implantation Am J Obstet Gynecol 115 101 1973
3 Haspels A A & Andriesse C The effect of large doses of estrogens post coitum in 2000 women Eur J Obstet Gynecol Reprod Biol 3 113 1973
4 Massey J B Garcia C R & Emich J P Management of sexually assaulted females Obstet Gynecol 38 29 1971
5 Kuchera L K Postcoital contraception with diethylstilbestrol JAMA 218 562 1971
6 Kuchera L K Postcoital contraception with diethylstilbestrol updated Contraception 10 47 1974
7 Rosenfeld D L Huggins G R Jusczyk Am García C R & Rickels K Medical psychologic and social factors in morning after pill utilization J Planned Parenthood Physicians 11 19 1976
8 Derogatis L R Lipman R S & Covi L The SCL 90 An outpatient psychiatric rating scale Psychopharmacol Bull 9 13 1973
9 Derogatis L R Rickels K & Rock A F The SCL 90 and the MMPI A step in the validation of a new self report scale Br J Psychiat 128 280 1976
10 Derogatis L R Lipman R S Rickels K Uhlenhuth E H & Covi L The Hopkins Symptom Checklist (HSCL) A self report symptom inventory Behav Sci 19 1 1974
11 Rickels K Garcia C R Lipman R S Derogatis L R & Fisher E L The Hopkins Symptom Checklist Assessing emotional distress in obstetric gynecologic practice Primary Care 3 751 1976
12 Derogatis L R Personal communication 1976

Submitted for publication September 7 1977

George R Huggins M D
Dept of Obstetrics & Gynecology
Family Planning Service
3400 Spruce Street
Philadelphia Pa 19104
USA

Acta Obstet Gynecol Scand 58 69–71 1979

PLASMA AND URINE LEVELS PRODUCED BY AN ORAL DOSE OF AMPICILLIN 0 5 G ADMINISTERED TO WOMEN TAKING ORAL CONTRACEPTIVES

Agneta Philipson

From the Department of Infectious Diseases Danderyd Hospital Danderyd and the Department of Clinical Pharmacology Karolinska Hospital Stockholm

Abstract Earlier studies have shown that ampicillin produces 50% lower—and therefore very likely less adequate—plasma levels in pregnant than in nonpregnant women The present investigation compares levels of ampicillin in plasma and urine produced by a single oral dose administered to 10 healthy women taking oral contraceptives on the 21st and on the 28th day of the menstruation cycle Plasma levels of ampicillin were lower on the 21st day than on the 28th i e a difference in the same direction as between pregnant and nonpregnant women although the difference was not significant Contrary to what was found for pregnant women the dose of ampicillin to women taking oral contraceptives does not have to be doubled in order to compensate for lower plasma levels

INTRODUCTION

Ampicillin administered to pregnant women has been shown to produce plasma levels that are about 50% lower than those produced by the same dose when given to the same women when not pregnant (?) The lower levels reached during pregnancy could be compensated for by doubling the ampicillin dose (3) The decrease in plasma levels of ampicillin was not correlated to the length of gestation or to the increase in body weight However the decrease paralleled an increase in distribution volume (V_D) and renal plasma clearance (Cl_R) and a decrease in the biological half life of ampicillin in pregnant as compared to in nonpregnant women (2)

The effect of oral contraceptives (o c) in many ways simulates pregnancy It is therefore of interest to know if similar differences in the above mentioned parameters for ampicillin exist in women taking o c as compared to women not taking o c

The present cross-over study was designed to compare levels of ampicillin in plasma and urine produced by a single oral dose of ampicillin administered to women on the 21st day of the o c cycle and levels produced by the same dose administered on the 28th day of the cycle In this fashion each woman was given one dose of ampicillin 0 5 g when under maximum influence of o c hormone and another also of 0 5 g when under supposedly less influence

MATERIAL AND METHODS

Ten women aged 20–3 years (mean ?5) volunteered for the study They were all healthy as judged by history physical examination and routine laboratory tests performed on blood and urine Their mean recorded body weight was 60 2 kg (S D 6 4 kg range 51–70 kg) All were taking o c of a combined type i e one pill taken daily for ?1 days followed by a pill free period of seven days Most subjects had been taking o c for more than three cycles Eight women were taking the same o c preparation (levonogestrel 0 25 mg ethinyloestradiol 0 05 mg Folinett Recip Sweden) and two were taking different preparations (levonogestrel 0.5 mg ethinyloestradiol 0 05 mg Follinyl Recip and lynestrenol 2 5 mg ethinyloestradiol 0 05 mg Lyndiol Novum Organon Netherlands)

Each woman was given two separate oral test doses (i e doses after which the levels of ampicillin in plasma and urine were followed) of commercial ampicillin administered as one tablet of 0 5 g (Doctacillin Astra Sweden) One test dose was given on the 1st day of the pill cycle and the other was given on the 28th day

None of the women had been taking any antibiotic for at least one month prior to the study and none was taking any medication other than o c Prior to administration of doses the women had been fasting for at least 8 h Food and drink were allowed 3 h after dose administration

The sampling schedule is shown in Fig 1 Further details as well as assay procedures have been described previously (?) The lowest measurable concentration of ampicillin in plasma varied between various assays from 0 0 to 0 06 μg/ml and in urine from 1 1 to 1 5 μg/ml

The area under the plasma concentration curve (AUC) (dimension h μg/ml) and Cl_R was calculated for each patient and dose as has been described earlier (?) Statistical analysis was performed by Student s *t* test for paired

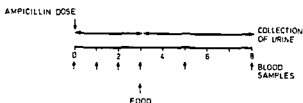


Fig 1 Sampling schedule for blood and urine and time for food intake in relation to administration of ampicillin test dose

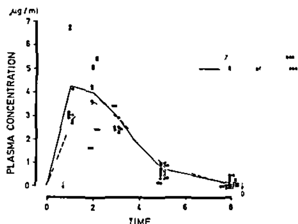


Fig 2 Mean plasma levels of ampicillin following a single oral dose of 0 5 g in 10 women taking o c

observations when these appeared to be normally distributed For clearly skewed observations statistical analysis was performed by sign test for paired observations Such data is indicated by ST in the table

RESULTS

Mean plasma levels of ampicillin produced by a single oral dose of 0 5 g in women taking o c on the 21st and 28th day of the o c cycle are shown in Fig 2 On the 21st day of the cycle plasma levels were *lower than on the 28th day at 1 2 3 and 8 h* although the difference was significant only at 1 h $P=<0.05$) Mean values for peak plasma levels UC Cl_R and recovery in urine of ampicillin are shown in Table I On the 21st day the mean values for peak level AUC Cl_R 0–8 h and recovery in urine were lower than on the 28th day but the differences were not significant

DISCUSSION

We have earlier reported that ampicillin administered intravenously as well as orally in single and multiple doses produces lower plasma levels in pregnant than in nonpregnant women (2) The difference in plasma levels of ampicillin produced in pregnant women was correlated to a significant change in various pharmacokinetic parameters for ampicillin during pregnancy These changes could largely be accounted for by well known alterations during pregnancy in various body functions such as increase of extracellular fluid and increase of renal function rather than to an increase in body weight and length of gestation

The trend in the difference between plasma levels of ampicillin on the 21st and 28th day of the o c cycle found in this study was the same as between plasma levels in pregnant and nonpregnant women (2) but less marked There was no tendency towards the difference being larger for lighter women than for heavier The lack of a more pronounced

Table I *Mean values for peak plasma levels AUC Cl_R and recovery in urine of ampicillin in 10 women taking o c*

NS=not significant ST=derived by sign test

	Peak (µg/ml)	AUC (µg/h)	Cl_R ml/min			Recovery in urine 0–8 h	
			0–3 h	3–8 h	0–8 h	mg	%/dose
21st day of o c cycle							
Mean	3 9	12 9	279	287	261	183 3	36 9
S D	1 4	5 8	141	232	165	96 8	19 4
28th day of o c cycle							
Mean	4 6	14 4	296	276	274	234 0	46 9
S D	2 0	5 9	251	109	200	164 0	37 8
	NS	NS	NS	NS ST	NS ST	NS ST	NS ST

difference may be due to lack of a significant difference *in alterations in body functions between the* 21st and 28th day It may also depend on a lack of alterations in pharmacologically pertinent body functions in women taking o c as compared to women not taking o c Another possible explanation might be that alterations induced by o c may not be fully reversed within the pill free period between the 21st and the 28th day O c of a sequential type has been shown not to alter extra or intracellular water significantly (1) Corresponding data for o c of combination type is lacking in the literature It is possible that a comparison between values for plasma levels and Cl_R reached by the same dose of ampicillin given to women before they even started taking o c and for instance on the 21st day of the third pill cycle would show a much more pronounced difference However the levels of ampicillin in plasma reached on the 21st day of the o c cycle in this study are sufficiently high compared to levels found in nonpregnant (2) women The difference does not appear clinically important and thus does not call for an extended study (or further investigation)

ACKNOWLEDGEMENT

The skillful technical assistance of Mr Anders Lindman is gratefully acknowledged

REFERENCES

1 Bladh W H Ledner M A & Tyler T Effect of oral contraceptives on body water and electrolytes J Reprod Med *13* 223 1974
2 Philipson A Pharmacokinetics of ampicillin during pregnancy J Infect Dis *136* 370 1977
3 Philipson A Plasma levels of ampicillin in pregnant women following administration of ampicillin and pivampicillin Accepted for publication in Am J Obstet Gynecol

Submitted for publication Nov 24 1977

Agneta Philipson
Department of Infectious Diseases
Danderyd Hospital
Danderyd Sweden

Acta Obstet Gynecol Scand 58 73–79 1979

HYPERTHECOSIS SYNDROME

Clinical Endocrinologic and Histologic Findings

K Karam and S Hajj

From the Department of Obstetrics and Gynecology American University of Beirut Hospital Beirut Lebanon

Abstract Five patients were found to have hyperthecosis ovarii as evidenced by the presence of large lipid containing thecal cells in the ovarian stroma The clinical picture was similar in all of them featuring mild virilization obesity and oligomenorrhea with refractoriness to clomid therapy Plasma FSH levels were low normal while LH levels were slightly elevated Urinary 17 ketosteroids levels were elevated and plasma testosterone concentrations were upper normal The response to dexamethasone suppression and HCG stimulation is discussed The effect of wedge resection on the clinical and endocrinologic pictures is evaluated

In 1935 Stein & Leventhal correlated a clinical syndrome of menstrual irregularity featuring amenorrhea a history of sterility masculine type of hirsutism and less consistently retarded breast development and obesity with a gross ovarian anatomical enlargement (21) Recently the P C O syndrome is considered to be a whole spectrum of clinical symptoms and signs ranging from oligoovulation to amenorrhea and hirsutism However in 1944 Goldzieher & Green (10) reviewed and published 1079 reported cases of P C O and infertility was the main complaint followed by obesity amenorrhea and hirsutism

The anatomical picture varies from normal sized ovaries to those bilaterally enlarged with thickened capsules (20) The histological picture varies from a thickened tunica with abundant large sub-capsular follicular cysts to a hyperplastic stroma with evident biological activity (11)

Predictability of clinical manifestations based on the histologic picture has been attempted but no constant relationship could be established between the two This has made the diagnosis of P C O a histologic one with a wide variety of clinical manifestations Inspite of the varying symptomatology patients of P C O have responded favorably to wedge resection With the recent introduction of clomid wedge resection has been replaced by this medical treatment giving the same results

Nevertheless there are some patients who respond to wedge resection after clomid failure Such patients are at one extreme of the spectrum exhibiting a specific histologic picture mild virilization and ovarian hyperresponsiveness to HCG measured by testosterone levels Included in the past under polycystic ovarian disease Culiner & Shipple (4) i 1949 classified them under hyperthecosis syndrome However the introduction of clomiphene citrate replacing wedge resection and their refractoriness to clomid therapy has brought hyperthecosis to the front again This paper attempts at studying the clinical endocrinologic and histologic features of five patients with this syndrome

METHODS AND MATERIALS

Case Reports

Case I A 35 year-old married lady was admitted to the medical service on July 4 1976 for a persistent headache of five years duration Having a normal blood pressure skull X ray and electroencephalogram she was referred to the reproductive endocrinology service because of oligomenorrhea since the age of 30 weight gain excessive hair growth and primary infertility with failure to respond to eight courses of clomid in progressive dose schedules up to 150 mg daily Physical examination revealed an obese lady weighing 205 pounds linear Ht 5 ft 2 in B P 130/80 mmHg Coarse hair was abundant over chin scattered over face with temporal hair recession and moderate frontal balding Breasts were well developed and pubic hair extended to the umbelicus with no clitoromegaly Ovaries could not be palpated Laboratory tests showed normal blood count electrolytes blood urea nitrogen serum proteins calcium cholesterol and triglycerides Normal thyroid function tests Normal IVP Gynecography revealed an enlarged right ovary 8×6 cm left 5 3×3 cm On July 17 after completion of the adrenal and ovarian function tests a laparoscopy confirmed the gynecograpic findings and a laparotomy was performed Both ovaries were enlarged with a hemorrhagic cyst measuring 5×5 cm in the right ovary Right oophorectomy and left ovarian wedge resection were performed Since

Acta Obstet Gynecol Scand 58 73–79 1979

HYPERTHECOSIS SYNDROME

Clinical Endocrinologic and Histologic Findings

K Karam and S Hajj

From the Department of Obstetrics and Gynecology American University of Beirut Hospital Beirut Lebanon

Abstract Five patients were found to have hyperthecosis ovarii as evidenced by the presence of large lipid containing thecal cells in the ovarian stroma The clinical picture was similar in all of them featuring mild virilization obesity and oligomenorrhea with refractoriness to clomid therapy Plasma FSH levels were low normal while LH levels were slightly elevated Urinary 17 ketosteroids levels were elevated and plasma testosterone concentrations were upper normal The response to dexamethasone suppression and HCG stimulation is discussed The effect of wedge resection on the clinical and endocrinologic pictures is evaluated

In 1935 Stein & Leventhal correlated a clinical syndrome of menstrual irregularity featuring amenorrhea a history of sterility masculine type of hirsutism and less consistently retarded breast development and obesity with a gross ovarian anatomical enlargement (21) Recently the P C O syndrome is considered to be a whole spectrum of clinical symptoms and signs ranging from oligoovulation to amenorrhea and hirsutism However in 1944 Goldzieher & Green (10) reviewed and published 1079 reported cases of P C O and infertility was the main complaint followed by obesity amenorrhea and hirsutism

The anatomical picture varies from normal sized ovaries to those bilaterally enlarged with thickened capsules (20) The histological picture varies from a thickened tunica with abundant large sub-capsular follicular cysts to a hyperplastic stroma with evident biological activity (11)

Predictability of clinical manifestations based on the histologic picture has been attempted but no constant relationship could be established between the two This has made the diagnosis of P C O a histologic one with a wide variety of clinical manifestations Inspite of the varying symptomatology patients of P C O have responded favorably to wedge resection With the recent introduction of clomid wedge resection has been replaced by this medical treatment giving the same results

Nevertheless there are some patients who respond to wedge resection after clomid failure Such patients are at one extreme of the spectrum exhibiting a specific histologic picture mild virilization and ovarian hyperresponsiveness to HCG measured by testosterone levels Included in the past under polycystic ovarian disease Culiner & Shipple (4) in 1949 classified them under hyperthecosis syndrome However the introduction of clomiphene citrate replacing wedge resection and their refractoriness to clomid therapy has brought hyperthecosis to the front again This paper attempts at studying the clinical endocrinologic and histologic features of five patients with this syndrome

METHODS AND MATERIALS

Case Reports

Case 1 A 35-year-old married lady was admitted to the medical service on July 4 1976 for a persistent headache of five years duration Having a normal blood pressure skull X ray and electroencephalogram she was referred to the reproductive endocrinology service because of oligomenorrhea since the age of 30 weight gain excessive hair growth and primary infertility with failure to respond to eight courses of clomid in progressive dose schedules up to 150 mg daily Physical examination revealed an obese lady weighing 205 pounds linear Ht 5 ft 2 in B P 130/80 mmHg Coarse hair was abundant over chin scattered over face with temporal hair recession and moderate frontal balding Breasts were well developed and pubic hair extended to the umbelicus with no clitoromegaly Ovaries could not be palpated Laboratory tests showed normal blood count electrolytes blood urea nitrogen serum proteins calcium cholesterol and triglycerides Normal thyroid function tests Normal IVP Gynecography revealed an enlarged right ovary 8×6 cm left 5 3×3 cm On July 17 after completion of the adrenal and ovarian function tests a laparoscopy confirmed the gynecograpic findings and a laparotomy was performed Both ovaries were enlarged with a hemorrhagic cyst measuring 5×5 cm in the right ovary Right oophorectomy and left ovarian wedge resection were performed Since

operation menstrual cycles became regular temperature charts biphasic and an endometrial biopsy was secretory She reported less frequent shaving of her facial hair Serum testosterone and urinary ketosteroids were normal one month after surgery The patient s headache persisted and was dismissed by neurologists as psychogenic

Case 2 H L A 30-year old lady was admitted to the reproductive endocrinology service on September 27 1976 because of oligomenorrhea obesity and hirsutism since menarche at 13 and amenorrhea of four years duration Married at the age of 28 she failed to get pregnant and consulted a gynecologist who started her on clomid therapy She took it on and off for four years at 50 and 100 mg dose schedules but failed to ovulate and her hirsutism persisted Physical examination revealed an obese muscular lady weighing 209 pounds and 5 feet 4 inches tall B P 120/80 mmHg She had coarse hair over face chest and abdomen with normal developed breasts and no clitoromegaly On pelvic examination she had bilaterally enlarged ovaries After completion of her ovarian and adrenal function tests a laparoscopy was performed on October 6 1976 that confirmed the diagnosis of polycystic ovaries which at laparotomy measured 6×5 cm each with thick capsules and no evidence of ovulation Bilateral wedge resection was done The tubes were normal One day following surgery on October 7 she had a menstrual flow that was followed by three regular menses in November December and January Her LMP was on January 9 1977 and EDC is on October 16 1977

Case 3 A [illegible] year-old married lady was admitted to the [illegible]ve endocrinology service on October 17 1976 [illegible]e of oligomenorrhea since her menarche at 13 [illegible]ity and hirsutism of six years duration Three years [illegible] to admission the patient started complaining of increased hair growth and an increase in weight with hoarseness of voice Admitted in 1973 baseline 17 ketosteroids 17 hydroxysteroids and testosterone were measured and the 17 hydroxysteroids and 17 ketosteroids suppressed well with dexamethasone but not testosterone The patient was put on enavid to no avail Clomid was given 100 mg P O daily for five days for three courses and 150 mg P O daily for three courses but she did not ovulate and was still oligomenorrheic so she was admitted for study

Physical examination revealed an obese muscular lady wt=183 pounds linear Ht 5 ft 2 in BP 115/70 Coarse hair was scattered over the face chin and chest wall with temporal hair recession Breasts were well developed She had no clitoromegaly Ovarian size could not be well assessed Laboratory tests showed normal blood count normal electrolytes calcium BUN and cholesterol normal thyroid function tests normal FBS and 2 h PC Skull X ray showed a normal sella turcica and an IVP was normal with no suprarenal enlargement She had a normal creatinine clearance rate After completion of her adrenal and ovarian function tests a laparatomy was performed on October 27 Both ovaries were enlarged measuring 7×5 cm each with thick shiny capsules and no evidence of ovulation Wedging of both ovaries was done Since operation her menstrual cycles became regular and hirsutism decreased Temperature charts over few months were biphasic

Case 4 A 27 year-old lady was admitted to the repr[illegible] ductive endocrinology service on October 17 1976 b[illegible] cause of oligomenorrhea since menarche at the age of 1[illegible] obesity and hirsutism of nine years duration Seen first [illegible] the outpatient clinic she was found to have elevat[illegible] plasma testosterone and urinary 17 ketosteroids Treat ment with enavid for two years regulated her menses but failed to affect her weight gain or facial hair growth Clomid in increasing dose schedules up to [illegible]00 mg daily for six courses failed to induce ovulation Physical examina tion revealed an obese muscular lady weighing 177 pounds and 5 ft 1 in tall B P 1?0/80 mmHg She had coarse hair over face and chin with normal developed breasts and pelvic hair extending to the umbelicus There was no clitoromegaly and pelvic examination revealed an enlarged left ovary Laboratory tests showed normal blood count electrolytes BUN serum proteins calcium cholesterol and triglycerides and normal thyroid function tests Gynecography done outside showed an enlarged left ovary Skull X ray and IVP were normal Ovarian and adrenal function tests were performed and the patient was discharged to be readmitted on November 17 1976 for a laparotomy Both ovaries were enlarged measuring 5×5 cm on the right and 6×5 cm for the left ovary They had thickened capsules with no evidence of ovulation Wedge resection was performed Since the operation her menses have been regular the hair growth regressed and her weight decreased to 147 pounds A premenstrual endometrial biopsy three months after surgery was secretory

Case 5 A 30-year-old lady gravida 1 para 1 was admitted to the medical endocrinology service in May 1975 because of oligomenorrhea obesity hirsutism and hoarseness of voice since the age of 25 She was found to have elevated 24 h urinary 17 ketosteroids of 29 8 mg and 17 hydroxycorticosteroids of 7 3 mg respectively Plasma testosterone was within normal limits 51 ng/100 ml Dexamethasone suppression test with 8 mg daily for three days brought the 17 ketosteroids down to 7 6 and hydroxysteroids to 1 5 mg/244 h respectively Plasma testosterone remained at 50 ng/100 ml The patient was discharged on enavid However she developed menometrorrhagia for which she underwent a D & C in a community hospital Her hirsutism did not improve She was admitted again in January 1975 to the gynecology service when an adrenal venography showed the venous distribution and size of the left adrenal to be normal The right adrenal vein could not be catheterized Testosterone level in the catheterized specimen was within normal (28 ng/100 ml) Suspected to have virilizing adrenal hyperplasia of adult onset an ACTH stimulation test was performed Synacthen 0 5 mg in 500 ml 5% D/W over 8 hours from 8 00 a m to 4 00 p m was given repeatedly over two days Baseline values for plasma cortisol were 6 5 μg% at 8 00 a m 17 ketosteroids and hydroxysteroids were 13 3 and 0 mg/24 h respectively The first day of ACTH stimulation yielded a plasma cortisol of 62 μg% at 4 00 p m and 24 h urinary 17 keto and hydroxysteroids of 27 7 and 47 mg respectively The second day of ACTH stimulation yielded a plasma cortisol of 69 μg% (morning level 19 μg%) and 24 h urinary 17 keto and hydroxysteroids of 22 5 and 32 8 mg respectively

Table I *Serum FSH and LH levels in five patients with hyperthecosis before and after ovarian wedge resection in MIU/ml*

	Before		After wedge resection	
	FSH	LH	FSH	LH
Case 1	7 7	0	5	9
Case 2	8	14	7 6	8
Case 3	7	18	6	9 2
Case 4	6 4	19 5 14 5	7 6	6 5 1 75
Case 5	6 25	16	6	16 4

She was discharged on prednisone 2 5 mg daily Clomid up to 150 mg daily received for five courses failed to induce ovulation

On November 28 1976 she was admitted to the reproductive endocrinology service because of persistent menometrorrhagia hirsutism and hoarseness of voice Physical examination revealed an obese muscular lady weighing 173 8 pounds and 5 ft tall B P 120/75 mmHg She had coarse hair over chin and face with no recession or baldness Breasts were well developed No humps striae or male hair distribution Ovaries could not be palpated because of obesity Laboratory tests showed normal blood count electrolytes BUN serum proteins calcium cholesterol and triglycerides and normal thyroid function tests After completetion of her ovarian function tests a laparotomy was performed on December 1 Both ovaries were enlarged to 6×5 cm each with thick shining capsules and no evidence of ovulation Bilateral wedge resection of the ovaries was done The patient s menses became regular and her hirsutism improved

Laboratory studies On admission to the reproductive endocrinology service of the American University Hospital each one of the five patients had the following tests done serum gonadotropins follicle stimulating hormone (FSH) and luteinizing hormone (LH) plasma testosterone (T) and two baseline determinations of 24 h urinary 17 ketosteroids (17 Ks) and 17 hydroxysteroids (17 OH) Dexamethasone was then given orally 2 mg every 6 h for four days During the last two days of Dexamethasone administration 5000 I U of human chorionic gonadotropin (HCG) were given intramuscularly each day Plasma T urinary 17 Ks and 170 H were measured daily Two days following wedge resection plasma FSH T and 24 h urinary 17 Ks and 17 OH were measured In case one these were repeated one month after surgery

Serum gonadotropins FSH and LH were measured by double antibody radioimmunoassay procedures (16 17) and all samples were performed in the same assay in duplicate The second International Reference Preparation of human menopausal gonadotropin was used as a reference standard for both the FSH and LH assays and expressed as M I U second IRP HMG per milliliter

Plasma T was measured by previously established radioimmunoassay procedures (6) and all samples were performed in the same assay in duplicate Urinary 17 Ks were measured by Drektu (5) technique and 17 OH were measured by the method of Reddy (19)

RESULTS

Gonadotropins The plasma FSH and LH levels are summarized in Table I FSH levels were normal in the five patients 7 7 8 7 6 4 and 6 25 MIU/ml respectively (normal follicular phase levels 5 to 15 MIU/ml) while LH levels were high at 20 14 18 19 5 and 16 MIU/ml (normal follicular phase levels 5 to 15 MIU/ml) Surgery had no effect on the FSH levels 5 7 6 7 2 and 6 MIU/ml while LH levels

Table II *Plasma testosterone concentrations in five patients with hyperthecosis in ng/100 ml*
Baseline levels Dexamethasone suppression HCG stimulation and wedge resection

	Baseline	2 days DM	5 000 IU HCG	5 000 IU HCG	2 days after wedge resection	1 month post-op
Case 1	41 41	40	80	84	31	21
Case 2	60 6	50	75	100	18	
Case 3	64 2 66	81	90	84	4	
Case 4	68 7	27	12 5	41	16	
Case 5	51 51	43	84	98	17	

Table III *Urinary 17 ketosteroids in five patients with hyperthecosis in mg/24 hours*
Baseline levels Dexamethasone suppression HCG stimulation and wedge resection

	Baseline	2 days DM	5 000 IU HCG	5 000 IU HCG	2 days after wedge resection	1 month post op
Case 1	17 4 16	6 2	2 6	5 2	12 7	13
Case 2	19 2 20	7	6	5 5	8	
Case 3	8 6 20	4 1	3 4	5 2	7 4	
Case 4	14 4 16	3 5	2 6	4	9	
Case 5	16 41 7	11 5	0 91	2 1	11 4	

dropped to 9 8 9 2 and 6 5 MIU/ml in the first four cases and remained unchanged 16 4 MIU/ml in case 5

Steroids Plasma T levels are summarized in Table II All five patients had normal levels of plasma T 41 41 60 62 64 2 66 68 72 and 51 51 ng/100 ml respectively (normal adult female levels 40–80 ng/100 ml) Two days of dexamethasone at 8 mg/d brought it down in cases one two four and five to 40 50 27 and 43 ng/100 ml respectively In case three it went up to 81 ng/100 ml Intramuscular administration of 5000 IU of HCG on two successive days resulted in a sustained increase in all of them to 80 84 ng/100 ml in case one 75 100 ng/100 ml in case two 90 84 84 ng/100 ml in case three 12 5 41 ng/100 ml in case four and 84 98 ng/100 ml in case five Two days following ovarian wedge resection in cases two three and four and left oophorectomy right wedge resection in case one T concentrations fell substantially in all to 31 18 24 16 and 17 ng/100 ml respectively One month after surgery case one still had low T at 21 ng/100 ml

17 Ks are summarized in Table III They were moderately elevated in all five patients at 17 4 16 19 2 20 8 6 20 14 4 16 and 16 41 7 mg/24 h (normal adult female levels 5 to 15 mg/24 hours) In all of them two days of dexamethasone at 8 mg/d produced only a partial suppression to 6 2 7 4 1 3 5 and 11 5 mg/24 h On the third day of dexamethasone subsequent to the intramuscular administration of 5000 IU of HCG their levels were low at 2 6 6 3 4 2 6 and 0 91 mg/24 h On the fourth day after the second HCG injection th

Table IV *Urinary 17 hydroxysteroids in five patients with hyperthecosis in mg/24 hours*
Baseline levels Dexamethasone suppression HCG stimulation and wedge resection

	Baseline	2 days DM	5 000 IU HCG	5 000 IU HCG	2 days after wedge resection	1 month post-op
Case 1 12 7	14 8 12 5	1 6	0	3 4	13	
Case 2	5 6 1	0	0	0	8	
Case 3	7 4 11 1	4	1 6	0 5	5 5	
Case 4	7 6 8	4 3	1 6	2 3	9	
Case 5	10 4 14 7	7 7	1 1	3 8	21	



Fig 1 Cystic follicle with a hyper plastic luteinized theca interna (original magnification H & E ←↶()

levels were slightly higher at 5 2 6 5 5 2 4 and 2 1 mg/24 h Two days following surgery the levels were within normal in all 12 7 8 7 4 9 and 11 4 mg/?4 h

17 OH levels are summarized in Table IV They were normal in cases two three and four at 5 6 1 7 4 11 1 and 7 6 8 mg/24 h In cases one and five they were slightly elevated to 14 8 12 5 and 10 4 14 7 mg/24 h (normal adult female levels 2 to 10 mg/24 h) On dexamethasone there was a normal decrease to 1 6 0 0 4 4 3 and 7 7 mg/24 h Following the first HCG administration the levels were low at 0 0 1 6 1 6 and 1 1 mg/24 h They were still low at 3 4 0 0 5 2 3 and 3 8 mg/24 h after the second HCG injection Two days following surgery the levels went up to 13 8 5 5 9 and 21 mg/24 h in all five cases

HISTOLOGY

The histologic picture was quite similar in all five cases A thick capsule that stained positively for collagen with trichrome stains Numerous primary follicles some of which had developed further into secondary follicles No mature graafian follicles or corpora lutea Atretic follicles were scattered in the parenchyma with multiple cystic follicles of varying sizes lined by granulosa cells and hyperplastic



Fig 2 Stromal thecomatosis Large cells with abundant acidophilic cytoplasm (original magnification H & E ×25)

luteinized theca interna (Fig 1) The stroma appeared hypercellular with focal areas of luteinization at a considerable distance from the cystic follicles (Fig 2) They consisted of large cells with abundant acidophilic cytoplasm occasionally vacuolated and round vesicular nuclei with prominent nucleoli

DISCUSSION

As early as 1943 the term hyperthecosis was used by Fraenkel (8) to describe nests of luteinized cells scattered throughout the ovarian stroma Later Morris & Scully (18) referred to cases where there was luteinization of the stroma as hyperthecosis ovarii Classified as a syndrome by Culiner & Shippel (4) Givens (9) and colleagues in 1971 published a study of two families with familial ovarian hyperthecosis and in 1973 Judd (12) and associates described a family of two siblings and their mother who had the disease In 1974 Farber (7) published a case report of hyperthecosis syndrome Karp & Herrmann (13) described it as a clinically severe variant of the polycystic ovary syndrome Massively obese very hairy women who lack signs of frank virilization save for occasional slight clitoromegaly or temporal balding

In accordance with the formentioned definitions we are reporting in the present paper five cases of hyperthecosis syndrome the clinical picture of which is obesity oligomenorrhea mild virilization (increased coarse hair growth hoarseness of voice and occasional temporal or frontal balding) and refractoriness to clomid therapy and histologic presence of large lipid containing thecal cells in clusters in the ovarian stroma at a considerable distance from the follicles

Gonadotropin profile showed asynchronously elevated LH concentrations with low normal levels similar to the levels reported by Yen (22) and Givens (9) and in contrast to the cases reported by Scully (3) and Judd (12)

Surgery had no immediate effect on FSH levels while LH concentrations dropped in four patients all of whom gained regular menstruation and one got subsequently pregnant In one case LH concentration was unchanged

Baseline plasma testosterone determinations were in the high normal range for all suppressed mildly on dexamethasone in four cases and were slightly raised in one while they all increased in response to HCG stimulation and decreased following wedge resection It becomes evident then as Bardin et al (1) demonstrated through ovarian vein catheterization that the source of elevated testosterone in patients with hyperthecosis syndrome is definitely ovarian The normal adrenal vein T concentration in case five (28 ng/ml) that was lower than her peripheral levels speaks also for a hyperactive ovarian stroma However since the purified level of T is a function of its production and metabolic clearance then it is due to an increase in the latter that at least one third of hirsute women will have normal peripheral testosterone levels as has been demonstrated by Bardin & Lipsett (2) and Judd (12) The equivocal decrease of plasma testosterone in four patients after dexamethasone is in accordance with Lipsett (15) Kirschner (14) and other investigators that dexamethasone can significantly suppress plasma testosterone of ovarian origin It is difficult to explain its rise in case three though we have to keep in mind the effect of body size and fat tissue mass on peripheral conversion of steroids and their metabolic clearance rates

Baseline urinary 17 ketosteroids were elevated in all five patients with a partial suppression on dexamethasone pointing towards an ovarian component in these elevated steroids which could not be sufficiently stimulated by HCG in the presence of dexamethasone suppression

Baseline urinary 17 hydroxysteroids were slightly elevated in two cases a finding not surprising in view of their greatly increased body bulk They were all adequately suppressed with dexamethasone in contrast to the poor suppressibility reported by Givens (9)

In all five patients wedge resection resulted in a significant reduction of plasma testosterone concentrations Clomiphene Citrate at increasing dose schedules had been tried in all of them for an adequate length of time but failed to induce ovulation. This could be explained on the basis of excessive potent ovarian androgens interfering with Clomid's action on the hypothalamus and/or estrogen effect on the growing follicles

Regular menstruation has occurred in all following surgery Case one who suffered of coarse hair growth over the face and frontal baldness had an improvement in hair growth evidenced by less frequent shaving while her baldness was unchanged although she recently reported less loss of scalp hair This is similar to the original report of

Fraenkel (8) on unilateral wedge resection and contralateral oophorectomy and its effect on hair growth Her plasma T concentration one month after surgery was normal and an endometrial biopsy was secretory Case two got pregnant three months after surgery She noted a significant reduction in hair growth over her face Case three was ovulating regularly as evidenced by her biphasic temperature charts She noted significant improvement in her voice and facial hair growth since surgery Case four reported an appreciable decrease in weight and hair growth An endometrial biopsy three months after surgery was secretory Case five noted favorable changes in voice and facial hair and her menses became regular

Recent replacement of wedge resection by medical induction of ovulation and the refractoriness of hyperthecosis patients to clomid therapy makes it imperative to differentiate them from those with polycystic ovarian disease and treat them separately The two entities overlap significantly in their clinical picture except for virilization that characterizes hyperthecosis patients Pathologically they are inseparable except for the histologic finding of lipid containing theca like cells in the ovarian stroma Endocrinologically they have the same steroidal and gonadotropin patterns While polycystic ovarian disease responds favorably to clomid therapy hyperthecosis patients do not They do well on wedge resection Whether to consider it as a separate entity or think of it as a clinically severe variant of the polycystic ovary syndrome is immaterial

ACKNOWLEDGMENTS

We are indebted to Dr Ibrahim Salti for the radioimmunoassay and to Dr Ramez Azoury for the pathology

REFERENCES

1 Bardin C W Lipsett M B & Edgcomb J H Studies of testosterone metabolism in a patient with masculinization due to stromal hyperthecosis N Engl J Med 277 399 1967

Bardin C W & Lipsett M B Testosterone and androstenedione blood production rates in normal women and women with idiopathic hirsutism and polycystic ovaries J Clin Invest 46 891 1967

3 Case Records of the Massachusetts General Hospital (Case 69–1972) N Engl J Med 287 1197 1972

4 Culiner A & Shippel S Virilism and theca cell hyperplasia of the ovary A syndrome J Obstet Gynaecol Br Emp 56 439 1946

5 Drektu I J Heisler A Scism G R Stern S Pearson S & McGavak T H The determination of urinary steroids The preparation of pigment free extracts and simplified procedure for the estimation of total 17 ketosteroids J Clin Endocrinol 12 55 1952

6 Durfau M L Catt K J Tsuruhara T & Ryan D Radioimmunoassay of plasma testosterone Clin Chim Acta 37 109 1972

7 Farber M Daoust P R & Rogers J Hyperthecosis syndrome Obstet Gynecol 44 35 1974

8 Fraenkel L Thecoma and hyperthecosis of the ovary J Clin Endocrinol 3 557 1943

9 Givens J R Wiser W L Coleman S A Wilroy R S Andersen R N & Fish S A Familial ovarian hyperthecosis Am J Obstet Gynecol 110 959 1971

10 Goldzieher J W & Green J A The polycystic ovary I Clinical and histologic features J Clin Endocrinol 22 325 1962

11 Green J A & Goldzieher J W The polycystic ovary Am J Obstet Gynecol 91 173 1956

12 Judd H L Scully R E Herbot A L Yen S S C Ingersol F M & Kliman B Comparison of endocrinologic and histologic findings with polycystic ovarian disease Am J Obstet Gynecol 117 976 1973

13 Karp L & Herrmann W L Diagnosis and treatment of hirsutism in women Obstet Gynecol 41 283 1973

14 Kirschner M A & Jacobs J B Combined ovarian and adrenal vein catheterization to determine the sites of androgen overproduction in hirsute women J Clin Endocrinol 33 199 1971

15 Lipsett M B & Korenman S G Androgen metabolism JAMA 190 757 1964

16 Midgley A R Radioimmunoassay for human follicle stimulating hormone J Clin Endocrinol Metab 27 295 1967

17 Midgley A R Radioimmunoassay a method for human chorionic gonadotropin and human luteinizing hormone Endocrinology 79 10 1966

18 Morris J M & Scully R E Nonneoplastic Abnormalities of the Ovary with Endocrine Effect 2 Endocrinology and Pathology of the Ovary 1st ed p 151 The C V Mosby Company St Louis 1958

19 Reddy W J Modification of the Reddy Jenkins Thorn method for the estimation of 17 hydroxy corticoids in urine Metabolism 3 489 1954

20 Smith K D Steinberger E & Perloff W H Polycystic ovarian disease Am J Obstet Gynecol 93 994 1956

21 Stein I F & Leventhal M L Amenorrhea associated with bilateral polycystic ovaries Am J Obstet Gynecol 49 181 1935

22 Yen S S C Vela P & Rankin J Inappropriate secretion of follicle stimulating hormone and luteinizing hormone in polycystic ovarian disease J Clin Endocrinol 30 435 1970

Submitted for publication Aug 26 1977

Karam S Karam M D
American University Hospital
Beirut Lebanon

Acta Obstet Gynecol Scand 58 81–85 1979

ACID–BASE BALANCE DURING LAPAROSCOPY

The Effects of Intraperitoneal Insufflation of Carbon Dioxide and Nitrous Oxide on Acid–Base Balance during Controlled Ventilation

Ricardo Magno Alf Medegård Rolf Bengtsson and Sven Erik Tronstad

From the Department of Anesthesiology and Department of Obstetrics and Gynecology Sahlgrenska Hospital Goteborg Sweden

Abstract During laparoscopy the carbon dioxide used to achieve a pneumoperitoneum is absorbed from the peritoneal cavity into the blood The object of the present study was to clarify certain aspects concerned with anesthetic and ventilatory techniques mostly in connection with the comparison between the effects of insufflation of either carbon dioxide or nitrous oxide Anesthesia included ventilation with a volume controlled ventilator in curarised patients Respiratory volumes were calculated according to the patient s body area The results show a sharp rise in P CO_2 and a fall in pH after intraperitoneal insufflation with carbon dioxide while no changes were observed when nitrous oxide was used The clinical consequences of these findings are discussed

Gynecological laparoscopy has become a routine procedure in order to secure a diagnosis avoiding an unnecessary laparotomy Laparoscopy requires a pneumoperitoneum and this is achieved by the insufflation of carbon dioxide (CO_2) A trocar is then introduced into the peritoneal cavity and through it the laparoscope Inspection of the pelvic abdomen can then be undertaken A steep Trendelenburg position is used to shake down the intestine away from the pelvic organs

The respiratory effects of the absorption of CO_2 from the peritoneal cavity into the blood stream have been studied previously either during general anesthesia with controlled and spontaneous respiration or during local analgesia (1 3 4 6 8 11) The effects of insufflation with nitrous oxide (N O) have been compared with those of CO_2 (2 13 16) The Trendelenburg position itself also affects respiration (14 15)

The various reports on the respiratory effects are generally consistent On the other hand the use of spontaneous respiration associated with depressant anesthetic drugs for patients awake in local analgesia or the use of controlled ventilation with fixed volumes without considering each patient s body area raised the question of how much influence these external factors may have had on the results It therefore seemed of interest to follow the effects of peritoneal insufflation of CO_2 and of N_2O using controlled ventilation by means of a ventilator in curarised patients under general anesthesia and above all using minute volumes calculated with a Nomogram so that the ventilation of different patients could be accepted as equivalent independent of each patient s body area

MATERIAL AND METHODS

Twenty four women were included in the present study their ages ranging from 17 to 35 years (mean 25 4) their weights from 38 to 81 kg (mean 56 3) and their heights from 1 47 to 1 73 m (mean 1 67) After giving their consent to the blood sampling they were chosen consecutively excluding those with cardiovascular or pulmonary disease They were allotted to one of two groups one with 13 women in whom the pneumoperitoneum was produced by CO_2 (called the CO_2 group) and the other with 11 women in whom N O was used for this purpose (N O-group)

Premedication Each patient was premedicated one hour prior to anesthesia with intramuscular diazepam (Valium Roche) and atropine sulphate according to body weight Patients were placed on the operating table in a horizontal lithotomy position This position was not changed during blood sampling

Anesthesia A standardized anesthesia technique was used An ultra short barbiturate (hexobarbitone sodium Evipan Bayer) served for induction followed by succinylcholine chloride (Celocurin Vitrum) for endotracheal intubation Anesthesia was maintained with 70% N_2O in oxygen and supplemented with meperidine hydrochloride Alcuronium chloride (Alloferin Roche) was used as muscle relaxant

Ventilation was controlled during the whole procedure with an Engstrom ventilator (volume controlled) by means of a non rebreathing system The respiratory minute volumes were calculated in relation to body area and according to Engström & Herzog s Ventilation Nomogram (7) so that all the patients would be ventilated alike ECG

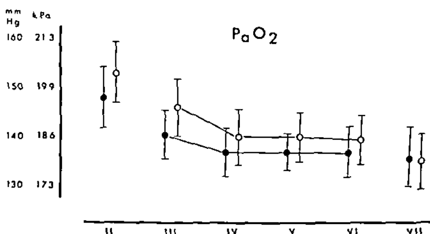


Fig 1 Oxygen tension values in the two groups studied (mean ±S E M) CO_2 group ●—● and N_2O group O—O Samples were taken from arterial blood Sample II was taken after 15 min ventilation (steady state) Sample III was taken immediately after insufflation was accomplished while samples IV–V–VI were obtained 5 10 and 15 min respectively after III Sample VII was collected 10 min after exsufflation The values in both groups are higher than normal There are no statistical differences either between the groups or within each group A slight decrease from II to VII can be observed

control by means of continuous recording was made in every patient during the procedure and the postoperative period

Blood sampling Seven samples were taken in each case the first (I) from arterialized capillary blood on the day prior to the operation and the following six samples during anesthesia from arterial blood collected through an indwelling catheter placed in a radial artery The second sample (II) was taken after 15 min of controlled ventilation (steady state) and immediately before the start of peritoneal insufflation The third sample (III) was taken immediately after insufflation was accomplished The fourth (IV) the fifth (V) and the sixth (VI) samples were drawn 5 10 and 15 min respectively after the third sample in order to follow the effects of the absorption of the gases from the peritoneum After blood sampling the laparoscopy was performed with the patient in a slight head down position and the peritoneal cavity was emptied thereafter Ten minutes later the seventh blood sample (VII) was taken Blood samples were collected in heparinised glass syringes and kept in iced water until analysed though not longer than one hour

Analysis for blood gases A Radiometer PHM 7? equipment with standard PO_2 and PCO_2 electrodes was used for the determinations of blood gases The base deficit (BD) value was calculated from the alignment nomogram (17) using PCO pH and the hemoglobin concentration

Statistical method The results were analysed with Compucorp 325 Scientist Student s *t* test was used for determining the significance of differences between mean values *p* values below 0 0_ were considered significant

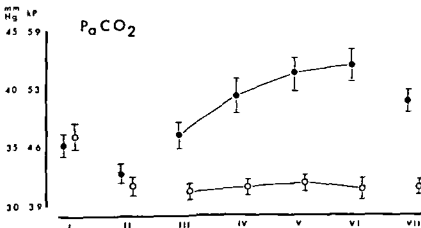


Fig 2 Carbon dioxide tension values in the two groups (symbols as in Fig 1) Sample I was taken from arterialized capillary blood on the day prior to operation The remaining samples are described in Fig 1 There are no changes within the N_2O group In the CO_2 group there is a statistically significant difference between II and VI as well as between II and VII The values from samples III–IV–V–VI–VII in the CO group are significantly higher than the corresponding values in the N O-group

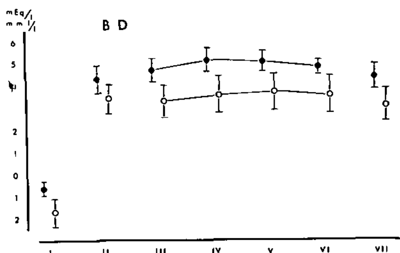


Fig 3 BD values in the two groups (symbols as in Figs 1 and 2) Apart the differences between sample I and the samples taken during anesthesia before and after insufflation in both groups there are no differences either between the groups or within each group

RESULTS

No complications were observed during the procedure Arterial blood pressure and pulse were stable the whole time ECG control during the procedure and recovery period showed no signs of arrhythmia or other disturbance

Twenty patients were insufflated with 4 0 to 4 5 l gas during a period of five minutes Of the four remaining two received 3 5 l and the other two 5 0 l according to their size

The oxygen tension levels in both groups are shown in Fig 1 as the mean values ±S E M during the procedures The values are higher than normal There are no differences between the groups A slight decrease can be seen in both groups from sample II to samples VI and VII though without statistical significance

The carbon dioxide tension values are presented in Fig 2 The results in the CO_2 group show a highly significant increase from 32 7 mmHg (3 95 kPa) ±0 87 (S E M) at sample II to 42 2 mmHg (5 48 kPa) ±1 37 at sample VI *p* value <0 001 This difference between II and VII is likewise highly significant (*p*<0 001) The results in the N O-group show no differences between II and VI or VII values

The P CO value at III in the CO group is higher than that in the N O group (*p*<0 01) while at IV V VI and VII the differences are even more pronounced (*p*<0 001)

The BD values are shown in Fig 3 The patients in both groups are more acidotic at II than on the day before op ration (I) The results of per operative sampling show no differences either within each group or between the groups

The pH values are illustrated in Fig 4 The val

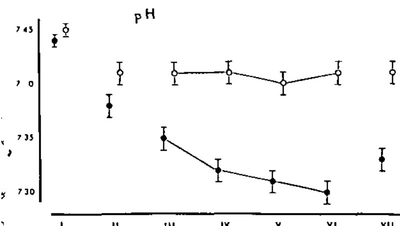


Fig 4 The pH values in the two groups studied (symbols as in Figs 1 and 2) While the values in the N O-group show no changes those in the CO_2-group display a statistically significant decrease from II to VI In spite of a recovery from VI to VII the difference between II and VII is still significant The values in the CO_2-group at III IV V VI VII are significantly lower than the corresponding values in the N O-group

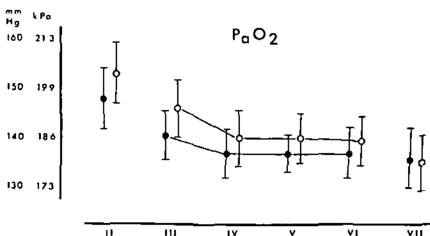


Fig 1 Oxygen tension values in the two groups studied (mean ±S E M) CO_2-group ●—● and N_2O group O—O Samples were taken from arterial blood Sample II was taken after 15 min ventilation (steady state) Sample III was taken immediately after insufflation was accomplished while samples IV–V–VI were obtained 5 10 and 15 min respectively after III Sample VII was collected 10 min after exsufflation The values in both groups are higher *than normal There are no* statistical differences either between the groups or within each group A slight decrease from II to VII can be observed

control by means of continuous recording was made in every patient during the procedure and the postoperative period

Blood sampling Seven samples were taken in each case the first (I) from arterialized capillary blood on the day prior to the operation and the following six samples during anesthesia from arterial blood collected through an indwelling catheter placed in a radial artery The second sample (II) was taken after 15 min of controlled ventilation (steady state) and immediately before the start of peritoneal insufflation The third sample (III) was taken immediately after insufflation was accomplished The fourth (IV) the fifth (V) and the sixth (VI) samples were drawn 5 10 and 15 min respectively after the third sample in order to follow the effects of the absorption of the gases from the peritoneum After blood sampling the laparoscopy was performed with the patient in a slight head down position and the peritoneal cavity was emptied thereafter Ten minutes later the seventh blood sample (VII) was taken Blood samples were collected in heparinised glass syringes and kept in iced water until analysed though not longer than one hour

Analysis for blood gases A Radiometer PHM 71 equipment with standard PO_2 and PCO_2 electrodes was used for the determinations of blood gases The base deficit (BD) value was calculated from the alignment nomogram (17) using PCO_2 pH and the hemoglobin concentration

Statistical method The results were analysed with Compucorp 325 Scientist Student s *t* test was used for determining the significance of differences between mean values *p* values below 0 05 were considered significant

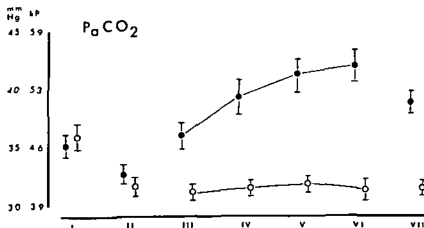


Fig 2 Carbon dioxide tension values in the two groups (symbols as in Fig 1) Sample I was taken from arterialized capillary blood on the day prior to operation The remaining samples are described in Fig 1 There are no changes within the N_2O group In the CO_2-group there is a statistically significant difference between II and VI as well as between II and VII The values from samples III–IV–V–VI–VII in the CO_2 group are significantly higher than the corresponding values in the N_2O-group

6 Desmond J & Gordon R A Ventilation in patients anaesthetised for laparoscopy Can Anaesth Soc J *17* 378 1970
7 Engstrom C-G & Herzog P Ventilation nomogram for practical use with the Engström respirator Acta Chir Scand Suppl 45 37 1959
8 Hodgson C McClelland R M A & Newton J R Some effects of the peritoneal insufflation of carbon dioxide at laparoscopy Anaesthesia *25* 38 1970
9 Kelman G R Swapp G H Smith I Benzie R J & Gordon N L M Cardiac output and arterial blood gas tension during laparoscopy Br J Anaesth *44* 1155 1972
10 Lenz R J Thomas T A & Wilkins D G Cardiovascular changes during laparoscopy Anaesthesia *31* 4 1972
11 Lewis D G Ryder W Burn N Wheldon J T & Tacchi D Laparoscopy—an investigation during spontaneous ventilation with halothane Br J Anaesth *44* 685 1972
12 Marshall R L Jebson P J R Davie I T & Scott D B Circulatory effects of carbon dioxide insufflation of the peritoneal cavity for laparoscopy Br J Anaesth *44* 680 1972
13 Marshall R L Jebson P J R Davie I T & Scott D B Circulatory effects of peritoneal insufflation with nitrous oxide Br J Anaesth *44* 1183 1972
14 Scott D B Lees M M & Taylor S H Some respiratory effects of the Trendelenburg position during anaesthesia Br J Anaesth *38* 174 1966
15 Scott D B & Slawson K B Respiratory effects of prolonged Trendelenburg position Br J Anaesth *40* 103 1968
16 Scott D B & Julian D G Observations on cardiac arrhythmias during laparoscopy Br Med J *1* 411 1972
17 Siggaard Andersen O Blood acid-base alignment nomogram Scand J Clin Lab Invest *15* 211 1963

Submitted for publication Dec 14 1977

Ricardo Magno M D
Department of Anesthesiology
Sahlgrenska Hospital
41345 Goteborg
Sweden

ANNOUNCEMENT

International Symposium on Endocrine Pathology of the Ovary will take place in Rosario Argentina May 23 26 1979 It is being organized by the Departments of Gynecology and Pathology of the Medical School National University of Rosario together with the Sociedad de Obstetricia y Ginecología de Rosario that celebrates its 40th Anniversary The subjects to be dealt with are

Development of the ovary
- Progress in light and electron microscopy of the ovary
Physiology of the ovary
Endocrine interactions of the ovary
Progress in the study of ovarian function
Clinical features of the different degrees of ovarian failure
- Severe ovarian insufficiency
Ovulation induction

To deal with these and related subjects a number of distinguished scientists have confirmed their assistance Among them are the following Professor Dr David Armstrong University of Western Ontario London Ontario Canada Professor Dr Robert Jaffe University of California San Francisco Professor Dr Edward Wallach University of Pennsylvania Professor Dr Luciano Zamboni University of California Los Angeles Professor Dr Santo Nicosia University of Pennsylvania Professor Dr Virendra Mahesh Medical College of Georgia Professor Dr Antonio Scommegna University of Chicago Professor Dr William Le Maire University of Miami Professor Dr Anne Colston Wentz University of Tennessee and Professor Dr Irwing Thompson Harvard Medical School

For information please contact
Dr Rafael Luis Pineda
Secretary Simposium Internacional sobre Fisiopatología Endocrina del Ovario
Santa Fe 1798
2000-Rosario Argentina

Acta Obstet Gynecol Scand 58 87 90 1979

SOME ADVERSE EFFECTS OF COPPER—IUD

Göran Cullberg and Bertil Larsson

From the Departments of Obstetrics and Gynecology East Hospital Gothenburg and Huddinge Hospital Huddinge Sweden

Abstract Perforations and extraction problems in some 30 700 women wearing a copper intrauterine device (Cu IUD) either a Cu 7 or Cu T have been studied Perforations were very rare Judging from the literature and the present investigation in cases of perforation the Cu 7 IUD has a tendency to penetrate the uterine wall and the Cu T IUD the cervical wall Retracted and detached strings were observed somewhat more often in women wearing Cu 7 IUD s The number of such cases was however not large enough to warrant a statistical comparison The cause of retention investigative procedures and recommendations in the removal of lodged Cu IUD s are discussed

The two copper intra uterine devices (Cu IUD s) Cu T IUD and Cu 7 IUD (Gravigard[R]) have now been widely used in Sweden for three and four years respectively The pregnancy rate is very low The continuation rate is high and side effects are very few (3 7)

The main reasons for removal are bleeding and pain The increased menstrual blood loss following insertion of a Cu IUD is however only moderate and considerably less than that induced by a plastic IUD (4) The frequency of genital infections in women using a Cu IUD is as low as 1 4 per cent (5) The above mentioned side effects are minor complications

However in the last few years scattered reports of more serious side effects have been related to the use of IUD s Thus 39 deaths in the US have been related to the use of plastic IUD s Of these women 35 had sepsis and 4 perforation and sepsis (9) Furthermore reports have appeared of perforations of the uterine wall by Cu IUD s and plastic IUD s without further complications (6 1) The wide acceptance of Cu IUD s for some years in Sweden prompted the present evaluation of the frequency of perforation and other serious complications connected with the insertion and removal of Cu IUD s

MATERIAL

The women included in the present retrospective study were admitted to either of the two Departments of Obstetrics and Gynecology in Gothenburg during 1974 and 1975 for removal of a Cu IUD During the two-year period 18 000 Cu 7 IUD s and 12 700 Cu T IUD s were used The number of removals (Cu 7 IUD s = 3 100 Cu T IUD s = 2 200) was estimated from a continuation rate of 83 per cent found by one of us in a separate study concerning two years use of Cu 7 IUD s in 357 women

RESULTS

The complications observed are summarized in Table I The frequency of perforations were found to be equal and low for the two types of Cu IUD s (3 perforations per type) but the uterine wall tended to be perforated more often by Cu 7 IUD s and the cervical wall more often by Cu T IUD s

Perforations In one woman the Cu 7 IUD had perforated the cervical wall and the string of the device was observed in the rectum through which the Cu 7 IUD was removed In two other patients the Cu 7 IUD had perforated the uterine wall and was shortly afterwards found to be embedded in the omentum The Cu 7 IUD s were easily removed via the laparoscope

In one case the Cu T IUD had perforated the uterine wall The device was removed without difficulty

Table I *Complications of insertion and removal of Cu IUD s*

	Cu 7 IUD	Cu T IUD
Number of Cu IUD s used in 1972—1975	18 000	12 700
Estimated number of removals	3 100	2 200
Perforations of the uterine wall	2	1
Perforations of the cervical wall	1	2
Lodged IUD with string torn or detached at removal	10	3
String not visible	21	2
IUD fractured at removal	1	0
Copper wire fractured	0	1

Table II *Perforations of Cu IUD s in the literature*

Author	Number of inserted Cu IUD s	Type of IUD	Site and frequency of perforation			
			Cervix		Corpus	
			n	%	n	%
Cederqvist *et al* (1975)	1 156	Cu 7	0	0	3	2 6
Cederqvist *et al* (1975)	1 153	Cu T	5	4 3	1	0 9
Rienprayura *et al* (1973)	1 120	Cu T	4	3 6	0	0
Williamson & Kirkland (1974)	3 000	Cu T	6	2 0	0	0
Tatum (1973)	5 000	Cu T	1	0 2	0	0
Present material	18 000	Cu 7	1	0 06	2	0 11
Present material	12 700	Cu T	2	0 16	1	0 08

via the laparoscope In two women the vertical limbs of Cu T IUD s were found to have penetrated the cervical wall but the string was retained in the cervical canal The device was removed by retracting it through the perforation of the cervical wall and then through the cervical canal

One of these Cu 7 IUD s had been inserted 10 weeks post partum None of the other perforations had occurred at insertion in connection with legal abortion or post partum

Cu IUD s stuck In one case a Cu 7 IUD inserted ~ years previously was very firmly lodged in the ne wall and on removal broke near the mush om tip at the junction of the vertical and horizontal arms One piece was left behind but was afterwards located by means of hysteroscopy and extracted from the myometrium

Detached strings At ten of the calculated 3 100 removals of Cu 7 IUD s and three of the calculated 2 200 of Cu T IUD s the device was firmly lodged and the string torn or detached In seven of these 13 cases the Cu IUD had been inserted in connection with legal abortions

Rectracted strings At removal of some 3 100 Cu 7 IUD s the string of 21 had retracted into the cavity The corresponding figures for the Cu T IUD were two out of 2 200

Fractured copper wire In one case a Cu T IUD used for two years was easily removed by pulling the string but the copper wire was found to be fractured and the plastic device somewhat eroded

DISCUSSION

In one of the series included in Table II perforation had occurred in three (0 26 per cent) of 1 156 insertions of Cu 7 IUD s (1) The corresponding total figures for the four published series in which Cu T IUD s had been used (Table II) were 17 (0 17 per cent) of 10 273 insertions In the present study however the rate of perforations was much lower viz 0 017 per cent and 0 024 per cent for Cu 7 IUD s and Cu T IUD s respectively All the perforating Cu IUD s were easily removed and the removal was not accompanied by any further serious complications This implies a very low risk of perforation by the two Cu IUD s concerned As for plastic IUD s estimated rates of perforations of 0 03 and 0 04 per cent for Lippes loop and Margulis coil respectively have been reported (8) The corresponding figures for Dalkon Shield were found to be 0 29 per hundred insertions (11) The difference in the commonest sites of perforation by the two IUD s is probably due to the differences in shape between the devices Moreover it has been postulated that the Cu T IUD is anchored in the uterine cavity by fixation of the transverse limb into the uterine wall (2)

Lodgement of Cu IUD s and detachment of strings at removal were observed somewhat more frequently for the Cu 7 IUD s The string of this IUD has now been replaced by one twice as strong However to avoid laceration of the cervix at removal of Cu IUD s by less experienced hands the string should not be fastened too firmly

In some cases the string could not be seen and had slipped into the uterine cavity This always occurs to some extent Judging from personal experience however it is advisable to leave a length of string corresponding to almost the depth of the vagina Such a procedure might be questioned from two points of view firstly the IUD could possibly be extracted in connection with the removal of a vaginal tampon secondly such a long string could possibly increase the risk of an ascending infection However no such ad

verse effects of a long string have been observed in our clinical studies

When extracting a Cu IUD the string should be gripped near the external cervical os and pulled in the direction of the uterine axis If the uterus is in strong ante or retroflexion it might be helpful to straighten the angle between the uterine cervix and corpus by pulling the portio in the direction of the vagina

When extraction is obstructed the string always breaks before the IUD Investigation of the causes of such obstructions should preferably be performed by hysteroscopy using Hyskon[R](Pharmacia Sweden) to give good visibility and accessibility to the uterine cavity Hysterography is rarely of greater benefit except when the IUD has perforated the uterine wall and then only to clarify the extrauterine location

When freeing a lodged Cu IUD dilatation of the cervical os is useful and the IUD can then be gripped by a straight forceps The IUD is then pushed inwards and rotated about half a turn around its long axis and then pulled out This manoeuvre usually liberates the partially perforating parts of the IUD

Thus in a series comprising a large number of insertions and removals the rate of major complications proved low and it is probably not possible to reduce it further by the use of any other intrauterine contraceptive method

REFERENCES

1 Cederqvist L L Lindhe B A & Fuchs F Perforation of the uterus by the Copper T and Copper 7 intrauterine contraceptive devices Acta Obstet Gynecol Scand *54* 183 1975

2 Kamal I Ghoneim M Talaat M & Mallawani A The anchoring mechanism of retention of the Copper T device Fertil Steril *24* 165 1973

3 Landesman R Kaye R E & Wilson K H A two-man experience with the copper T' intrauterine device Contraception 7 477 1973

4 Larsson B Hamberger L & Rybo G Influence of copper intrauterine contraceptive devices (Cu IUD) on the menstrual blood loss Acta Obstet Gynecol Scand *54* 315 1975

5 Larsson B & Wennergren M Investigation of a copper intrauterine device (Cu IUD) for possible effect on frequency and healing of pelvic inflammatory disease Contraception *15* 143 1977

6 Ledger W J & Willson J R Intrauterine contraceptive device The recognition and management of uterine perforations Obstet Gynecol *28* 806 1966

7 Newton J Elias J McEwan J & Mann G Intrauterine contraception with the copper 7 Evaluation after two years Br Med J *3* 450 1974

8 Peel J & Potts M *In* Textbook of contraceptive practice p 144 Cambridge University Press 1970

9 Population Reports Intrauterine devices Ser B No 2 p 35 37 1975 Department of Medical and Public Affairs The George Washington University Medical Center Washington

10 Rienprayura D Phaosavasdi S & Somboonsuk A Cervical perforation by the copper T intrauterine device Contraception 7 515 1973

11 Snowden R & Williams M The use effectiveness of the Dalkon Shield in the United Kingdom Contraception 7-91 1973

12 Tatum J H Metallic copper as an intrauterine contraceptive agent Am J Obstet Gynecol *117* 602 1973

13 Williamson H O & Kirkland B T Presentation at 12th Annual Meeting of Planned Parenthood Physicians Memphis Tennessee 1974

Submitted for publication June 15 1977

Göran Cullberg M D
Department of Obstetrics and Gynecology
Östra Sjukhuset
S-416 85 Göteborg
Sweden

ANNOUNCEMENT

Xth World Congresss on Fertility and Sterility The International Federation of Fertility Societies will sponsor the Xth World Congress to be hosted by the Spanish Fertility Society at the National Palace of Expositions and Congresses in Madrid Spain September 20 26 1980

There will be two days for Pre Congress Symposiums and Post Graduate Courses followed by a program on the following themes

- Spermatogenesis
- Ovulation
- Psychosexual and social aspects of fertility
- Problems of gamete transportation
  Immunology in reproduction
- *Controle of fertility*
  Neuroendocrinology of reproduction
- Fertilization and implantation
  Environmental and iatrogenic aspects of reproduction
- Genetics in reproduction

Please reply to
A Campos da Paz
Chairman Scientific program
Av Copacabana 664 AP 606
Rio de Janeiro Brazil

Postgraduate course in reproductive endocrinology The Department of Obstetrics and Gynecology of the Vrije Universiteit Amsterdam The Netherlands is holding a post graduate course in Reproductive Endocrinology on February 15 16 1979 The course is especially designed for use in day to-day clinical practice and will contain topics such as

Physiology and pathology of the menstrual cycle
Ovulation induction and hirsutism

On a limited basis participants will be given the oppurtunity to present actual case histories to a panel for discussion

Lecturers
Georgeanna S Jones M D Norfolk Va U S A
Griff T Ross M D Ph D Bethesda Md U S A
Howard W Jones Jr M D Norfolk Va U S A
Marc L Hermite M D Brussels Belgium
J Schoemaker M D Amsterdam The Netherlands

For further information please contact
Ms Th M Benning
Department of Obstetrics and Gynecology
Academisch Ziekenhuis Vrije Universiteit
De Boelelaan 1117
1081 HV Amsterdam The Netherlands

Acta Obstet Gynecol Scand 58 91-94 1979

MENTAL FACTORS INFLUENCING RECURRENCE OF STRESS INCONTINENCE

A Öbrink P Fedor Freybergh M Hjelmkvist and G Bunne

From the Department of Obstetrics and Gynaecology Karolinska Institutet Sabbatsberg Hospital Stockholm Sweden

Abstract At a recent follow up of 51 women operated on for stress incontinence there was an astonishingly high discrepancy between symptoms claimed by the patients and signs found by the physician To examine the influence of certain mental factors on the recurrence of stress incontinence the patients in the above mentioned follow up were tested with the Eysenck Personality Inventory test and the Sabbatsberg Depression Self rating Scale test The women with symptoms but no objective signs of stress incontinence showed a higher degree of both neuroticism and depression than the women of perfect health Thus in this group it may be a question of aggravation of symptoms which cannot be helped by a reoperation Instead these women might need psychiatric attention to relieve their psychosomatic symptoms

Surgical treatment for stress incontinence is mostly successful i e the social handicap is abolished However great efforts can often provoke urinary leakage postoperatively (8) Normally this is not enough to require further medical attention At a recent follow up of 51 women operated on for stress incontinence with pubococcygeal repair *ad modum* Ingelman Sundberg between 1955 and 1965 it became obvious that sometimes the patients own histories did not conform with the clinical findings (5) Two groups of women were remarkable one because symptoms of leakage were claimed without signs and the other because symptoms were absent in spite of clinically apparent stress incontinence The latter group does not pose a problem to the physician whereas the former group does Women in the former group will insist on further treatment and will not be content with the operation performed even though it seems totally successful from the physicians point of view Therefore it seems justifiable to seek a mental explanation for the discrepancy between signs and symptoms Therefore most women in the follow up were also submitted to two psychological tests namely the Eysenck Personality Inventory test (2) and the Sabbatsberg Depression Self rating Scale test (3 4) These tests reveal the degree of neuroticism (disposition to react in a neurotic way) and the degree of depression respectively Because of the diagnostic challenge and the risk of a hazardous reoperation solely based on the patient s complaints interest centred on those women who complained of stress incontinence but in whom no clinical signs of this could be verified

MATERIAL AND METHOD

Thirty three women mean age 65 years were examined 10–20 years after pubococcygeal repair for stress incontinence Preoperatively all patients had been thoroughly examined and severe genuine stress incontinence had been diagnosed At follow up visit the patients histories were scrutinized regarding the degree and the duration of a possible recurrence of stress incontinence A gynecological examination was performed and continence was checked with 250 ml saline solution in the bladder in the supine position The women were divided into four groups (see Fig 1)

1 free from symptoms and signs of stress incontinence
2 symptoms but no signs
3 signs but no symptoms
4 both symptoms and signs

The psychological examination included two tests

I The Eysenck Personality Inventory test (EPI) This test includes 57 questions to be answered with yes or no The degree of neuroticism introversion and extroversion can be estimated Only the subscale for neuroticism was used in this study and the evaluation was done according to the Stanine score We regard the so-called neuroticism in the Eysenck scale as a disposition of the isolated personality to react more or less neurotically in a situation of internal or external frustration Whether this disposition is based on the constitution of the personality or whether it is flexible and variable in different situations is unclear However it seems as if neuroticism might be influenced by an altered situation or (4)

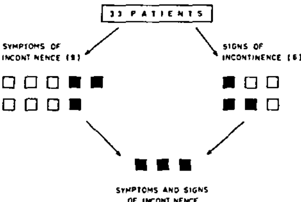


Fig 1 Distribution of the tested patients regarding symptoms and signs of stress incontinence

2 Sabbatsberg Depression Self Rating Scale (SDSRS) is based on 50 statements each with four possible answers such as never seldom often always The statements might be formulated like this I have a bad conscience without knowing why This test was performed at the medical examination and the data were computed and scored 1-25 It was thereby possible to make a semi-quantitative assessment in order to estimate e degree of depression

RESULTS (Figs 1 and 2)

Group 1 (neither symptoms nor signs) 21 women concentrated in the middle of the scales for both neuroticism and depression

Group 2 (symptoms but no signs) 6 women showed a high score regarding both neuroticism and depression

Group 3 (signs but no symptoms) 3 women showed a low degree of both neuroticism and depression

Group 4 (both symptoms and signs) 3 women scored the same as group 2

DISCUSSION

The tests reflect not only the tendency to mental aberrations in basic personality but also the response to environmental stress factors Therefore in spite of a perfectly normal personality a woman may have test results pointing to an increase in both neuroticism and depression in a situation of mental stress such as urinary leakage This is probably what happened to the women with both symptoms

Fig 2 Degree of neuroticism according to EPI Note the difference between patients with and without symptoms of stress incontinence

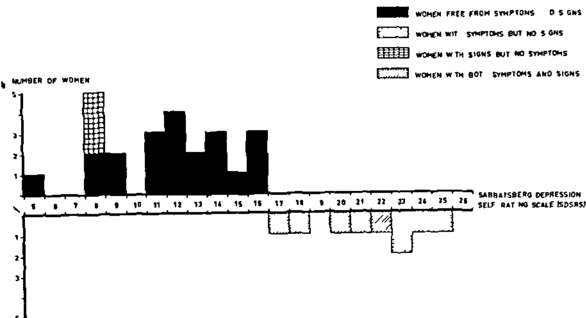


Fig 3 Degree of depression according to SDSRS Note the difference between patients with and without symptoms of stress incontinence

and signs (see Figs 1 and 2) As could be expected the continent women without symptoms showed a normal pattern concerning both neuroticism and depression

Some women obviously had stress incontinence although they denied symptoms These women had the lowest degree for both neuroticism and depression The most likely explanation for this dissimulation is that these women had arranged their daily lives so that sudden efforts and thereby urinary leakage were avoided as much as possible

Those subjects free from signs of urinary leakage at stress even though symptoms were claimed had a higher degree of both neuroticism and depression Thus these women were peculiar in the sense that no objective signs of incontinence could explain the test results All of them were entirely continent even under maximum effort with a full bladder no downward rotation of the bladder neck region was seen This does not however exclude incontinence of a very low degree such as a slight urinary leakage upon heavy straining in the standing position As a matter of fact this type of stress incontinence is very common in postmenopausal women in general and is present in a large percentage also postoperatively as has been shown by simultaneous urethrocystometry (1 8) It is therefore highly likely that this slight and very common form of urinary leakage is used by the patients in this group to gain advantages and resolve mental frustration The point is that if the bladder neck is well elevated and a firm floor is established underneath the urethra postoperatively and leakage cannot be provoked nothing can be gained by repeat operation (1 7 8) The exaggerated complaints of the patients will remain the same In fact there is a risk of more scarring and denervation as a result of renewed surgery so that an obvious and socially embarrassing recurrence might appear (1 6) The treatment of choice for these women is without doubt psychiatric

CONCLUSION

If a recurrence of stress incontinence cannot be verified clinically and there are no signs of technical failure of the previous operation it may be wise to hesitate to perform a repeat operation Instead the patients might be helped by psychiatric care to relieve neurotic and depressive symptoms

REFERENCES

1 Bunne G & Öbrink A Influence of pubococcygeal repair on urethral closure pressure at stress Accepted for publication in Acta Obstet Gynecol Scand 1977

2 Eysenck N H J & Eysenck S B G The Manual for the Eysenck Personality Inventory University of London Press London 1964
3 Fedor Freybergh P Hjelmqvist M & Zador G Psychodiagnostic follow up of Neovletta—a new low dose oral contraceptive Acta Obstet Gynecol Scand Suppl *54* 1976
4 Fedor Freybergh P The influence of oestrogens on the well being and mental performance in climacteric and postmenopausal women Acta Obstet Gynecol Scand Suppl *64* 1977
5 Öbrink A Pubococcygeal repair ad modum Ingelman Sundberg A retrospective investigation with 10–20 years time of observation Acta Obstet Gynecol Scand *56* 391 1977
6 Öbrink A Bunne G Ingelman Sundberg A & Ulmsten U The urethral pressure profile before during and after pubococcygeal repair for stress incontinence Acta Obstet Gynecol Scand *57* 49 1978
7 Öbrink A Bunne G Ingelman Sundberg A Pressure transmission to the pre urethral space in stress incontinence Accepted for publication in Urol Res 1977
8 Öbrink A Bunne G The margin to incontinence after three different operations for stress incontinence Accepted for publication in Scand J Urol Nephrol 1977

Submitted for publication N vember 9 1977

Anders Öbrink
Kvinnokliniken
Sabbatsbergs sjukhus
Box 6401
S 113 8? Stockholm
Sweden

Acta Obstet Gynecol Scand 58 95–99 1979

PLASMA MEDROXYPROGESTERONE ACETATE LEVELS FOLLOWING INTRAMUSCULAR OR ORAL ADMINISTRATION IN PATIENTS WITH ENDOMETRIAL ADENOCARCINOMA

T Laatikainen U Nieminen and H Adlercreutz

From the Departments I and II of Obstetrics and Gynaecology and the Department of Clinical Chemistry University Central Hospital Helsinki Finland

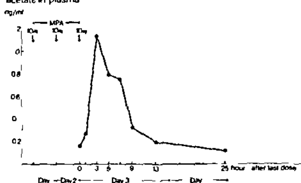
Abstract The concentration of medroxyprogesterone acetate (MPA) in plasma samples taken 24 h after intramuscular or oral administration of 100 mg daily doses of the drug to patients with endometrial adenocarcinoma was measured by radioimmunoassay In general a plasma level of about 4 ng/ml was found 24 h after the dose independent of the route of drug administration However in three of the patients to whom intramuscular MPA was given considerably higher values were found A maximal plasma level was achieved three hours after ingestion of 100 mg MPA This was followed by a rapid decline to 70–75% of the peak value after about 12 h A rather small day to-day intraindividual variation was found in daily blood samples taken just before administration of the next dose However considerable differences were found between individuals and it is concluded that this variation in plasma levels may be reflected in the clinical efficacy of the treatment Thus further studies in which plasma values and clinical effectiveness are correlated seem to be indicated

The treatment of patients with recurrent or advanced endometrial adenocarcinoma with progestin has been found to cause regression of tumour growth in a considerable proportion of cases (2 10 11) It has been proposed that the response of endometrial carcinoma to treatment with these steroids is related to its progestin binding capacity (5) which in turn depends upon the concentration of a specific binding protein (7) The effect of progesterone on endometrial carcinomatous tissue in *vitro* has been found to be closely correlated to the concentration of this steroid in the medium (13) The clinical efficacy of progestin treatment of endometrial carcinoma therefore may depend at least to some degree on the blood progestin level and its availability to the tumour tissue Measurements of the plasma level of these drugs during treatment may therefore be of value but the levels must first be correlated with clinical effectiveness

Medroxyprogesterone acetate (17α acetoxy 6α methyl 4 pregnene 3 20-dione (MPA) has been used widely for the treatment of advanced endometrial adenocarcinoma There are however very few reports on blood levels in the human and those available deal mainly with the administration of the steroid for contraceptive purposes (3 4 6 8) It was therefore decided to measure plasma MPA levels in patients with endometrial adenocarcinoma following both intramuscular and oral administration of the drug Day to-day variation and diurnal variation of plasma MPA levels were also investigated The results demonstrate a 10- to 100-fold difference in MPA concentration in individual patients who received the same dose However the mean plasma level observed was approximately the same after either oral or intramuscular injection of the steroid

MATERIAL AND METHODS

Patients 17 patients in whom endometrial cancer had been diagnosed by curettage were treated with a daily dose of 100 mg of MPA administered intramuscularly at 8 00 a m Blood samples were withdrawn into heparinized tubes in the morning before administration of the next dose the plasma separated by centrifugation and stored at −20°C until analysed These patients were then treated with pre operative radium followed by hysterectomy A second group of nine patients whose endometrial cancer was ultimately similarly treated received oral MPA for at least one month The group was subdivided as follows MPA 100 mg as a single dose administered to five patients 100 mg twice daily to three patients and one subject was given 100 mg of MPA three times daily The morning dose was given at 8 00 the mid-day dose (to the last patient) at noon and the evening dose at 16 00 The blood samples were always taken in the morning just prior to drug administration In this way the minimum level of MPA in plasma was monitored In one patient the plasma MPA concentration was measured 1 3 5 7 13 and 24 h after both a single dose of 10 mg and a



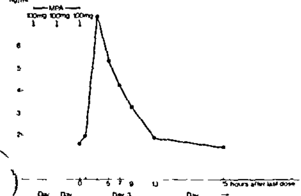


Fig 1 Plasma concentration of medroxyprogesterone acetate in a woman who received 10 mg oral doses of the drug at 24 h intervals on days 1 2 and 3 and 100 mg doses at 24 h intervals on days 5 6 and 7 The plasma measurements were made over a 24 h period after ingestion of the last 10 mg dose (upper panel) and over a similar period after ingestion of the last 100 mg dose (lower panel)

single dose of 100 mg MPA Eleven of the subjects were receiving digitalis for heart failure and nine were receiving various antihypertensive drugs those receiving any other treatment e g antibiotics were excluded from the study

Method Plasma MPA was determined by radioimmunoassay as previously described (17) using an anti MPA 3-(0-carboxymethyl)oxime bovine serum albumin serum (16 goat) kindly donated to us by Dr H J Rall Upjohn International Inc Kalamazoo Michigan 1 2 ^{3}H MPA (S A 58 Ci/mmol) obtained from New England Nuclear (Boston Mass) was used as an internal standard in the radioimmunoassay Chromatographic mass spectrometric and mass fragmentographic studies revealed the presence of large amounts of MPA metabolites in plasma which cross react with the antiserum It was also found that previously published methods in which the same antiserum had been used (4 6) resulted in gross overestimation of the MPA levels due to the assay being carried out directly on unextracted serum (4) or a too polar solvent being used for extraction (6) In our studies petroleum ether (b p 30-60°C Mallinkrodt St Louis Missouri) was used for extraction and this gave an over estimation of MPA of only 15% greatest in the samples drawn 7–24 h after drug administration Because of this it was felt to be unnecessary to include a chromatographic step The intra assay and inter assay coefficient of variation were 4 7% and 11% respectively in the concentration range 2–7 ng/ml All assays were carried out in duplicate

RESULTS

Plasma concentrations of MPA following intramuscular administration are shown in Table I The values shown represent minimum plasma concentrations as the samples were taken 24 h after injection i e just prior to re injection In three patients (nos 2 4 and 5) exceptionally high levels

Table I *Plasma concentrations of MPA after daily intramuscular administration of a 100 mg dose of MPA*

The injection was given at eight o clock a m and the blood sample taken before administration of the next dose

Case no	Age (y)	Weight (kg)	Day of MPA treatment	Serum concentration of MPA (ng/ml)
1	49	71	2	5 2
			5	2 5
			6	3 4
2	91	50	9	35 4
			13	46 7
			14	44 1
3	67	75	2	2 4
			3	5 3
4	69	68	13	12 3
			17	17 5
			18	24 8
5	50	55	7	19 9
6	57	69	4	5 7
7	5[illegible]	61	2	4 7
8	65	71	[illegible]	4 3
			6	7 1
9	68	71	2	4 3
			6	7 1
10	61	71	3	5 6
11	75	71	8	5 7
			9	6 3
			23	6 8
12	54	76	4	2 6
			5	2 2
13	74	79	7	4 5
14	67	77	2	3 5
15	68	79	[illegible]	3 8
16	74	79	3	3 [illegible]
17	72	76	8	0 4

Table II *Plasma concentrations of MPA after oral administration of one to three ×100 mg of MPA daily for at least one month*

Plasma samples were taken before giving the morning dose

Case no	Age (y)	Weight (kg)	Daily dose of MPA	Serum concentration of MPA (ng/ml)	Mean ± S E M
12	54	76	1×100 mg	3 0	
				3 5	
				3 5	
				3 4	
				3 2	
				4 2	3.5±0 17
13	74	79	1×100 mg	3 3	
				3 3	
				3 5	
				5 0	
				5 2	
				3 9	4 0±0 34
17	7_	76	1×100 mg	5 8	
				3 2	
				3 9	
				5 5	
				3 8	
				4 7	4 5±0 42
18	78	79	1×100 mg	2 8	
19	87	60	1×100 mg	7 4	
				5 1	
				5 4	
0	72	111	2×100 mg	7 0	
				7 8	
1	67	55	2×100 mg	1 1	
				0 7	
				0 5	
[illegible]	69	71	2×100 mg	6 7	
3	79	77	3×100 mg	8 4	
				9 9	
				8 4	

re found When these cases were excluded the mean 24 h level in the remaining patients was 4 2 ng/ml

In one patient the plasma concentration of MPA was monitored throughout a 24 h period after oral administration of 10 and 100 mg doses Following a rapid increase in plasma concentration a maximum value was seen in the sample taken at 3 h (Fig 1) Plasma concentrations following oral administration of MPA to the second group of patients are shown in Table II The mean 24 h value for the five patients who had received a 100 mg dose was 4 1 ng/ml In the first three patients (nos 12 13 and 17) the day-to-day variation of serum 24-h MPA values was studied in six sequential daily plasma samples The coefficient of variation calculated from these values was 12 21 and 22% respectively In these three cases plasma MPA levels were also measured earlier after intramuscular administration of the same dose (Table I) Lower 24-h values following intramuscular administration were found in two cases (nos 12 and 17) and a similar value in one case (no 13) When 200 mg (cases nos 20–23 Table II) or 300 mg (case no 23) of MPA were given orally a higher mean plasma value was found except in one case (no 21) in whom the values were exceptionally low

The effect of the progestagen on the carcinomatous endometrial tissue was evaluated in four of the patients (no 12 Table I nos 18 20 and 23 Table II) on whom hysterectomy was performed close to the time of plasma MPA measurement In these subjects the tissue specimen was adequately preserved despite preoperative radium treatment In all these cases a marked progestational effect was observed

DISCUSSION

Previous studies in dogs have shown that direct radioimmunoassay of MPA in plasma gives values 5–10 times greater than those obtained by gas liquid chromatography (6 9) Hiroi et al (6) obtained plasma levels approximately one fifth of those of Cornette et al (4) using corresponding doses of MPA by extracting the plasma with benzene iso-octane (2 1 v/v) The latter authors were aware of the fact that they also measured some metabolites Further chromatographic and radioimmunological studies in this laboratory revealed that the extraction technique used by Hiroi et al (6) gives an overestimation of more than 90% in samples taken 12–24 h after drug administration When the values obtained in the present investigation are compared to those presented by Hiroi et al (6) it can be clearly seen that they are lower This is in agreement with the results of our methodological studies which showed an overestimation of only 15% in samples (concentration about 4 ng/ml) for which a 93% overestimation was obtained using the procedure of Hiroi et al (6) Thus it would seem that values obtained for plasma MPA by different methods are uncomparable if the assay procedures are not identical Recently Jeppsson & Johansson (8) published a method almost identical to that used in the present investigation they also used petroleum ether for extraction and the same antiserum However they did not report any methodological investigations and their values can not be compared with those presented here as the mode of administration of MPA was different However it is reasonable to assume that the methods give identical results

After oral administration of MPA a maximum plasma concentration was found in the sample taken at 3 h (no samples were taken between one and 3 h) this was followed by a decline in plasma concentration (Fig 1) This plasma curve is similar to those published by Hiroi et al (6) The minimum plasma MPA concentration i e that measurable just before administration of the next dose was chosen for investigation in this study The day to-day variation of this value was rather small The MPA values were of the same order whether the single 100 mg dose was given intramuscularly or orally although in three patients in the former group exceptionally high levels were found perhaps due to a slower metabolic clearance rate of MPA in these subjects

MPA is effectively metabolised with the metabolites being conjugated with glucuronic acid and excreted mainly in urine (14) It is likely that individual differences exist in the absorption and/or metabolism of MPA with resulting differences in blood levels and—further—in its availability to the tumour tissue In this study considerable individual differences in the 24 h plasma levels of MPA were found This is in agreement with the results of a previous study (1) on the absorption of megestrol acetate (MA) a progestin with a structure closely related to that of MPA The individual variation in plasma levels of MA in a similar group of patients was of the same magnitude as that observed in the present study We think therefore that further investigation is indicated in which plasma MPA levels would be monitored during treatment of advanced or recurrent endometrial adenocarcinoma and related to the effectiveness of treatment

ACKNOWLEDGEMENTS

The excellent technical assistance of Mrs Helena Lindgren Miss Leena Tuomi Miss Inga Wiik and Mrs Anja Koskela is gratefully acknowledged This investigation was in part supported by grants from the Ford Foundation New York

REFERENCES

1 Adlercreutz H Nieminen U & Ervast H S J Steroid Biochem 5 619 1974
2 Bonte J Decoster J M Ide P Wynants P & Billiet G Excerpta Medica Internat Congr Series 379 285 1974
3 Bonte J B Drochmans A & Ide P Acta Obstet Gynecol Scand 45 121 1966
4 Cornette J C Kirton K T & Duncan G W J Clin Endocrinol Metab 33 459 1971
5 Haukkamaa M Karjalainen O & Luukkainen T Am J Obstet Gynecol 111 205 1971
6 Hiroi M Stanczyk F Z Goebelsmann U Brenner P F Lumkin M E & Mishell D R Jr Steroids 26 373 1975
7 Janne O Kontula K & Vihko R Acta Obstet Gynecol Scand Suppl 51 28 1975
8 Jeppsson S & Johansson E D B Contraception 14 461 1976
9 Kaiser D G Carlson R G & Kirton K T J Pharm Sci 63 420 1974
10 Kelley R M & Baker W H New Engl J Med 264 216 1961
11 Kistner R W Griffiths C T & Craig J M Cancer 18 1563 1965

1 Martin F & Adlercreutz H *In* Symposium on the Pharmacology of Steroid Contraceptive Drugs (ed S Garattini) Raven Press 1977 p 99
13 Nordqvist S Acta Obstet Gynecol Scand Suppl 19 75 1972
14 Slaunwhite W R & Sandberg A A J Clin Endocrinol Metab 21 753 1961

Submitted for publication May 20 1977

T Laatikainen M D
Department of Obstetrics and Gynaecology
Universitetscentralsjukhuset
SF-00290 Helsinki Finland

ANNOUNCFMENT

International Symposium on Human Placenta Proteins and Hormones is to be held at the University of Siena Italy July 4 7 1979

Scientific Committee Arnold Klopper Aberdeen Scotland Pier Giorgio Crosignani Milan Italy and Andrea Genazzani Siena Italy

Sponsors C N R Project Biology of Reproduction Italian Societies of Obstetrics Gynaecology and Endocrinology Serono Symposia Biodata

Topics

New placental proteins chemistry assay biological and clinical significance

Newly discovered placental β-endorphin

Physiology in mother and fetus of placental protein and steroid hormones

- Correlations between morphology and endocrine placental activity

Physiological variability of endocrine indices

Placental provocative tests

- Integrated use of endocrine and physical parameters in clinical practice

Mechanism involved in the initiation of labor

Lactogenic hormones and mammary glands during pregnancy and post partum

Round Table Clinical use of endocrine indices — critical evaluation

Invited Speakers

M Aubert Geneva Switzerland P Bischof Aberdeen Scotland H Bohn Marburg F R Germany T Chard London England P Crosignani Milan Italy G De Virgilus Milan Italy F Fraioli Rome Italy F Fuchs New York U S A A Genazzani Siena Italy P Keller Zürich Switzerland A Klopper Aberdeen Scotland A Liotta New York U.S A G Mandruzzato Trieste Italy C Robyn Brussels Belgium A Scommegna Chicago U S A Y Tatarinov Moscow USSR A C Turnbull London England G R Wilson Aberdeen Scotland

Official languages English and Italian

Researchers are invited to submit 250 word abstracts of unpublished work for oral or poster presentation before April 15 1979 A limited number of free communications will be selected for presentation and published with the invited lectures in the proceedings by Academi Press Abstracts of invited lectures free communications and posters will be published in a separate volume

Scientific Secretary

Professor A R Genazzani
Cattedra di Patologia Ostetrica e Ginecologica
Via Paolo Mascagni 46
53100 SIENA Italy
Tel 0577/49706 44051

International Symposium on Adrenal Androgens is to be held at the University of Siena Italy October 7 9 1979

Scientific Committee A R Genazzani Siena Italy G Giusti Florence Italy P C MacDonald Dallas U S A W D Odell Torrance U S A P K Siiteri San Francisco U S A J H H Thijssen Utrecht Holland A Vermeulen Ghent Belgium

Sponsors The American Express Company under the auspices of the Italian Society of Obstetrics and Gynaecology the Italian Society of Endocrinology the Italian Society of Fertility and Sterility and the C N R project Biology of Reproduction

Topics

- Androgen secretion by human adrenal and testis cells in culture
- Hormonal factors controlling and stimulating adrenal androgen secretion

Adrenal androgen metabolism and conversion in humans

Adrenal androgens in pregnancy in prepuberty puberty adult life ageing and in postmenopausal women hirsute and obese subjects

Enzymatic adrenal defects

Adrenal androgens and endometrial cancer

- Adrenal androgen effects on bone metabolism and on the hypothalamus pituitary gonadal axis

Round Table Adrenal androgens the future

Invited Speakers G Abraham Rolling Hills U.S A D Anderson Manchester England A Genazzani Siena Italy G Giusti Florence Italy P MacDonald Dallas U S A A Neville Sutton England B Nordin Leeds England W Odell Torrance U S A C Pintor Cagliari Italy J Poortman Utrecht Holland M Serio Florence Italy P Siiteri San Fransisco U S A P Sizonenko Geneva Switzerland J Thijssen Utrecht Holland D Tulchinsky Boston U S A A Vermeulen Ghent Belgium

Official language English

Researchers are invited to submit 250 word abstracts of unpublished work for oral or poster presentation before June 15 1979 A limited number of free communications will be selected for presentation and published with the invited lectures in the proceedings Abstracts of invited lectures free communications and posters will be published in a separate volume

Scientific Secretary

Professor A R Genazzani
Centro di Fisiopatologia della Riproduzione
Università di Siena
Via Paolo Mascagni 46
53100 SIENA Italy
Tel 0577/49706 44051

Acta Obstet Gynecol Scand 58 101–104 1979

SQUAMOUS CELL CARCINOMA IN SITU FROM THE UTERINE CERVIX TO THE DISTAL END OF THE FALLOPIAN TUBE

Reijo Punnonen Matti Gronroos and Pekka Vaajalahti

From the Departments of Obstetrics and Gynecology and Pathological Anatomy Turku University Turku Finland

Abstract An unusual case of squamous cell carcinoma of the uterine cervix is described in which spread occurred intraepithelially along the endometrium and one of the fallopian tubes This marked superficial extension is an example of abnormal spread of a malignant tumour whose prognostic significance is unknown

Carcinoma of the cervix usually spreads *per continuitatem* in the direction of the vagina or invasively to the local lymph nodes Intraepithelial carcinoma or preinvasive change is typically found in the marginal epithelium of the area showing invasive changes Rarely the spread is in the direction of the endocervix and even more rarely it continues upwards to the endometrium or mucosa of the tube An unusual case is presented in which a squamous cell carcinoma of the cervix spread as a carcinoma in situ along the endometrium to the distal part of the fallopian tube

CASE REPORT

A 64 year old previously healthy woman was found to have a Papanicolaou class III smear on routine examination in August 1976 There was no history of pregnancy or previous operations The menopause occurred when she was 52 there was no post menopausal haemorrhage At colposcopy diffuse inflammation was found on the ectocervix and there was a small transformation zone in the external os with atypically branching terminal vessels A biopsy from the latter area showed carcinoma in situ epithelii portionis On gynaecological examination the size of the uterus was consistent with the patient s age two small myomas were found in the fundus There were no other abnormal findings

Laparotomy was performed in October 1976 The macroscopic findings in the uterus were consistent with the findings of the previous gynecological examination The right tube was however moderately thickened and hyperaemic There was a small smooth thin walled cyst in the right ovary The left tube and ovary appeared normal The regional lymph nodes were not enlarged There were no palpable abnormalities of the intra abdominal organs There was no evidence of ascites or adhesions A right salpingectomy was performed The tube contained serous fluid in which there were granular particles Tuberculosis was suspected clinically During the operation the tube was sent for microscopical examination (frozen sections)

The tube was cut in three parts and two vertically cut pieces were studied in frozen sections Normal tubal mucosa could not be identified Instead the mucosa showed papillary folds and was covered by mildly variable squamous epithelium Everywhere the epithelial cells had a disorderly arrangement and the polarity was in general severely disturbed In many places no differentiated layers of epithelium could be seen There was cellular atypia and several mitotic figures were seen even in the higher epithelial layers The basal cell layer was uniform and no invasion could be shown There were no signs of a specific inflammation These findings were interpreted as squamocellular carcinoma in situ of the epithelium of the uterine tube

At operation the uterus both ovaries and the left tube were removed and sent for routine histological investigation The uterus was cut in two halves along its longitudinal axis and was transversely sectioned serially at intervals of three millimetres In the cervical areas no normal epithelium could be seen

The epithelium was squamous of variable height and extended as invasive islands or cords into the



Fig 3 A detail of the tubal epithelium where the cellular disorder nuclear atypia and frequent mitoses are evident ×87

stroma Keratinization cellular atypia and increased mitotic activity were conspicuous in these areas but no microinvasion from the solid tumour islands could be seen A diagnosis of invasive squamous cell carcinoma of the uterine cervix was made

In the serially sectioned specimens of the uterine corpus the mucosa was covered by stratified squamous epithelium showing often keratinization of individual cells severe cellular atypia and some mitotic figures This kind of epithelial structure was also seen in many of the more superficial glands

Fig 1 The endometrium is covered by a multilayered atypical squamous epithelium In general the endometrium is atrophic and some (for this state) normal glands can be seen At lower left atypical epithelium is seen inside a superficial gland but there is no invasion ×35

Fig 2 A papillary fold of the tubal mucosa The highly atypical epithelium is sharply demarcated everywhere ×87

but there was no invasion of the endometrial stroma or myometrium (Fig 1)

The right tube was similarly sectioned serially and at every level the epithelium showed the structure seen in the original specimen as described above (Figs 2 and 3) In one section however beneath an area resembling in situ a small lumen was seen covered by a very normal looking epithelium

The left tube was normal in structure Both ovaries had a degenerative stroma with post menopausal changes In the right ovary a serous cyst was seen but no trace of tumour tissue could be found In the uterine myometrium some partly fibrotic leiomyomas were also diagnosed

The histological diagnoses were Carcinoma squamocellulare in situ endometrii et mucosae tubae uterinae dextrae Cysta serosa ovarii dextri Leiomyomata uteri

After the operation liver scan lymphoscintigraph and lymphogram were all normal The patient received 5800 rads of telecobalt treatment to the pelvis region and is now asymptomatic

DISCUSSION

We have discovered only one similar case in the literature (8). This was a case of intraepithelial carcinoma of the cervix which had spread to the tube via the endometrium as in our own case. In addition there has been published recently a case in which carcinoma in situ of the fallopian tube was associated with cervical carcinoma (3). So far the mechanism of extraordinary active *per continuitatem* spread has been as difficult to explain as is the development of malignant degeneration in squamous metaplasia of the endometrium. It has always been accepted that the basal membrane presents the weakest barrier to the malignant neoplasm spread occurring through this into the stroma. In the present case the chronological sequence has apparently been progressive involvement of ectocervix, endocervix, endometrium and tubal mucosa. Definite stromal invasion could only be seen in the region of the ectocervix. Corresponding premalignant or intraepithelial carcinomatous lesions may be found in the marginal areas of invasive endometrial carcinoma (7). It is generally known, however, that primary carcinoma of the tube is quite rare. Moore & Enterline (4) consider that tubal proliferative lesions are most frequently due to inflammatory changes and only rarely does carcinoma in situ occur. Pauerstein & Woodruff (5) state that mitotic activity is an essential criterion for the diagnosis of carcinoma in situ of the tube. In our own case numerous mitoses were found in the tubal epithelium.

The prognostic significance of spread of carcinoma of the cervix to endometrium is unclear, for example in the FIGO international classification (1) it is not mentioned. According to Perez et al. (6) spread of cervical carcinoma to the endometrium worsens the prognosis. In the present case we were unable to demonstrate extrapelvic spread on the basis of laparotomy, lymphoscintigraphy, lymphography, liver scan and other routine procedures. Nevertheless the patient received external megavoltage therapy because of the danger of microinvasion, as Davy et al. (2) have recommended following hysterectomy.

REFFRENCES

1. Annual Report on the Results of Treatment of Carcinoma of the Uterus, Vagina and Ovary. FIGO 1974.
2. Davy M, Bentzen H & Jahren R. Simple hysterectomy in the presence of invasive cervical cancer. Acta Obstet Gynecol Scand 56: 105, 1977.
3. Mendez J A, Bedoya J M Jr, Matilla A, Nogales F Jr & Galera H. Carcinoma in situ of the fallopian tube associated with cervical carcinoma. Int J Gynaecol Obstet 14: 353, 1976.
4. Moore S & Enterline H. Significance of proliferative epithelial lesions of the uterine tube. Obstet Gynecol 45: 385, 1975.
5. Pauerstein C J & Woodruff J C. Cellular patterns in proliferative and anaplastic disease of the fallopian tube. Am J Obstet Gynecol 96: 498, 1966.
6. Perez C A, Zivnuska F, Askin F, Kumar B, Camel H M & Powers W E. Prognostic significance of endometrial extension from primary carcinoma of the uterine cervix. Cancer 35: 1493, 1975.
7. Ritzmann H. Types of endometrial hyperplacia and their relationship to carcinoma of the endometrium. Second International Meeting on Endometrial Cancer and Related Topics. St Thomas Hospital, London 1977.
8. Weill S, Prade M & Goldfart E. Epithélioma pavimenteux intra épithélial étendy á toute la surface de la cavité uterine et à la surface d'une trompe. Rapport d'un cas. Rev Fr Gynecol Obstet 63: 211, 1968.

Submitted for publication Nov. 25, 1977

Reijo Punnonen
Department of Obstetrics and Gynecology
University Central Hospital
SF 20520 Turku 52
Finland

Acta Obstet Gynecol Scand 58 105–113 1979

A CARD SORT METHOD FOR PAIN ASSESSMENT IN GYNAECOLOGY A MULTIDIMENSIONAL APPROACH

A E Reading Christine Reed and J R Newton

From the Departments of Psychological Medicine and Obstetrics and Gynaecology King s College Hospital Denmark Hill London England

Abstract This paper considers the problem of measuring the subjective report of pain In view of the limitations of existing approaches an alternative method of pain assessment is proposed This approach derives from a multidimensional concept of pain The test is in the form of pair comparisons and is designed to measure different pain dimensions Sufficient consensus was found over the meaning and relevance of words describing intrauterine device related pain and primary dysmenorrhoea to allow a standard test to be developed The reliability of the test was found to be high and its clinical advantages promising It was not possible to provide an adequate evaluation of the test s validity In view of these findings a longer term treatment evaluation study is currently being undertaken in order to establish this

The development of suitable assessment methods is a prerequisite to the effective control and measurement of pain It follows that pain cannot be said to be relieved if it cannot be measured The meagre potency of many analgesics compared with placebo demands that the measurement should be both accurate and sensitive (1) This paper will address itself to the problem of assessing the subjective report of pain as other pain indices such as behavioural or autonomic lend themselves to well established forms of measurement Moreover ultimately the physician must rely on what the patient tells him to assess the intensity as well as the efficacy of therapy (2) Most studies provide little information on subjective pain description beyond the simple mild moderate severe form Davidson & Neufold (3) comment this is surprising in view of the fact that the description of pain is a daily concern for the practising physician and verbal self reports are the most frequently measured response in experimental and clinical studies

It is clear that any attempt at pain measurement should be predicated on an understanding of the nature of pain It appears that a multi-dimensional concept of pain provides the most complete account Three main dimensions—sensory affective and evaluative—have been described (4) It therefore follows that severe limitations on the understanding of pain are imposed by measures—such as unidimensional rating scales—which treat pain as a single sensory quality varying only in intensity These scales constitute the most frequently employed method of pain assessment (5)

Given the need to treat pain as a multidimensional phenomenon the problem becomes one of devising reliable and valid measuring instruments capable of assessing the relevant facets of the pain experience In view of the limitations of existing methods of pain assessment this paper outlines an alternative assessment method and presents the results from a preliminary evaluation of a multidimensional approach to pain The object of the study was the assessment of primary dysmenorrhoea and intrauterine device (IUD) related pain Both pains are exceedingly common (7) and constitute a problem in their own right as distinct from pain which serves as a signal of some underlying pathology requiring treatment

METHOD

This method of pain assessment consisted of an adaptation of a technique developed by Shapiro (8) It is in the form of pair comparisons Its proposed use requires a range of statements which describe pain For each statement describing pain two additional statements indicating lesser degrees of pain are formulated Each of these additional words or statements should indicate different amounts of pain in the following proportions

(i) the original pain statement

(ii) improvement statement designed to indicate improvement but continued discomfort

(iii) a statement indicating minimal discomfort It is

Table I *Melzack and Torgerson checklist*

Part A

1	2	3	4
Flickering	Jumping	Pricking	Sharp
Quivering	Flashing	Boring	Cutting
Pulsing	Shooting	Drilling	Lacerating
Throbbing		Stabbing	
Beating		Lancinating	
Pounding			

5	6	7	8
Pinching	Tugging	Hot	Tingling
Pressing	Pulling	Burning	Itchy
Gnawing	Wrenching	Scalding	Smarting
Cramping		Searing	Stinging
Crushing			

9	10	11	12
Dull	Tender	Tiring	Sickening
Sore	Taut	Exhausting	Suffocating
Hurting	Rasping		
Aching	Splitting		
Heavy			

13	14	15	16
Fearful	Punishing	Wretched	Annoying
Frightful	Gruelling	Blinding	Troublesome
Terrifying	Cruel		Miserable
	Vicious		Intense
	Killing		Unbearable

17	18	19	20
ing	Tight	Cool	Nagging
idiating	Numb	Cold	Nauseating
Penetrating	Drawing	Freezing	Agonising
Piercing	Squeezing		Dreadful
	Tearing		Torturing

Part B *How does your pain change with time?*
Which word or words would you use to describe *the Pattern of your pain?*

1	2	3
Continuous	Rhythmic	Brief
Steady	Periodic	Momentary
Constant	Intermittent	Transient

intended that each triad of statements will reflect different pain dimensions

In order to develop a standard questionnaire certain conditions have to be met It is necessary therefore to be consensus over both the kind of words chosen to describe pain in a particular context and also the meaning or degree of pain that is commonly attached to these words Provisional support for this comes from a study carried out by Melzack & Torgerson (9) where it was found

1) that there are many words in the English language to describe pain

2) there is a high level of agreement that the words fall into classes or subclasses that represent particular dimensions or properties of pain

3) substantial proportions of the words have the same relative positions on a common intensity scale for people with divergent backgrounds

The first stage in the development of the card sort assessment consisted of identifying commonly used adjectives to describe intrauterine device related pain and primary dysmenorrhoea this has been previously reported by us (10)

Pain assessment—stage I

A checklist of words identified by Melzack and Torgerson (9) (see Table I) was distributed to Caucasian women experiencing or having experienced IUD related pain or primary dysmenorrhoea at King s College Hospital Family Planning and Gynaecology clinics The forms were administered by research nurses Women were required to circle words which described the pain that they had experienced Space was provided for the inclusion of additional words A total of 130 women with IUD related pain and 118 with primary dysmenorrhoea completed the forms

Results The distribution of word choices with patient groups and the frequencies with which the words were chosen are shown in Table II Other information collected has been reported elsewhere (10) It can be seen that only 9 and 11 words respectively were not chosen by any of the women in either group—dysmenorrhoea and IUD related respectively These totals increase to 28 and 26 respectively when words checked by less than three women are considered In other words less than 3% of the sample felt these words described the pain they had experienced

This survey was designed to establish the degree of consensus over the use of words to describe pain The viability of the proposed method of pain assessment will depend on consensus being found In evaluating these findings it is necessary to consider two points Firstly no restriction was placed on the number of words that each woman could choose Therefore some words could have been chosen despite being peripheral to the description of the pain under investigation Secondly many of the words were highly similar in meaning It is felt that these two factors can be taken as operating to attenuate the degree of consensus In view of this a number of words were extracted on the basis of their frequency of selection The next step in the development of the pain questionnaire consisted of establishing the degree of consensus over the meaning or intensity of pain attached to each of the words

Pain assessment—stage II

Words identified from stage I as being commonly used descriptors of period pain were randomly ordered against 5 point rating scales and distributed to Caucasian women attending Family Planning clinics Subjects were required to indicate the degree of pain that each word suggested to them on the 5 point scale provided The forms were administered by research nurses Completed forms were obtained from 35 women

Results The means and standard deviations for each word is presented in *Table III On the basis of the mean* scores and standard deviation for each word a classification was imposed on them This classification had the purpose of grouping words according to pain dimension For example the temporal dimension of pain was reflected by such words as brief intermittent constant The classification wherever possible reflected the frequency of word choice in stage I and the intensity scores established

Table II *Frequency of word choices for both patient groups*

DYS=dysmenorrhoea IUD=intrauterine device

Part A	DYS	IUD		DYS	IUD		DYS	IUD		DYS	IUD
1			2			3			4		
Flickering			Jumping	1	2	Pricking	5	3	Sharp	23	20
Quivering			Flashing	1	3	Boring	11	8	Cutting	11	4
Pulsing	4	6	Shooting	26	17	Drilling	2	2	Lacerating	2	2
Throbbing	29	11				Stabbing	28	13			
Beating		1				Lancinating		1			
Pounding		3									
5			6			7			8		
Pinching	2	3	Tugging	9	5	Hot	7	7	Tingling		
Pressing	6	8	Pulling	18	14	Burning	7	6	Itchy	2	1
Gnawing	17	12	Wrenching	9	5	Scalding		1	Smarting		2
Cramping	63	36				Searing	5	5	Stinging	2	1
Crushing		1									
9			10			11			12		
Dull	24	24	Tender	12	7	Tiring	32	23	Sickening	37	12
Sore	9	7	Taut	4	2	Exhausting	16	15	Suffocating	0	4
Hurting	7	9	Rasping								
Aching	54	40	Splitting	2	2						
Heavy	40	77									
13			14			15			16		
Fearful		3	Punishing	2		Wretched	7	5	Annoying	19	23
Frightful	4		Gruelling	8	6	Blinding	2		Troublesome	8	13
Terrifying	1	1	Cruel	2	3				Miserable	62	12
			Vicious	3	2				Intense	15	10
			Killing	4					*Unbearable*	10	12
17			18			19			20		
Spreading	2	4	Tight	10	5	Cool	2		Nagging	21	18
Radiating	7	3	Numb	2	1	Cold	6	4	Nauseating	25	7
Penetrating	11	15	Drawing	10	15	Freezing	3		Agonising	5	5
Piercing	6		Squeezing	2	2				Dreadful	4	2
			Tearing	3	4				Torturing	1	2

in stage II The aim was to arrive at three words or groups of words for each dimension each reflecting pain of different proportions to ensure minimal overlap within each triad (see Table IV)

Pain assessment—stage III

The foregoing research has established that there is a high level of consensus over both the choice of words used to describe pain as well as the level of pain that these words indicate A classification was then imposed on these words so that they were grouped into triads Each was chosen to reflect a pain dimension and each word within each dimension (triad) to indicate a different level of pain intensity

A pilot study was carried out in order to investigate the clinical utility of this method of subjective pain assessment Its aim was to establish the relevance of the words included in the test and the degree of consensus over meaning—i e to check the scaling that had been carried out The test consists of a set of cards upon each of which is a pair of words or statements one above the other in balanced order to remove the effects of position set Only statements concerned with a given dimension are paired There are three cards related to each dimension as each of the three words is compared with the other two A separate judgement is made for each pair

The pain questionnaire was administered to Caucasian women experiencing period pain The assessment was carried out either by the senior author or research nurse in the Family Planning clinics In addition to the card sort *patients were asked to complete a symptom checklist (see* Table V) which consisted of rating a number of possible pain effects (behavioural somatic mood cognitive and autonomic) in terms of occurrence The card sort was administered first Patients were instructed to indicate which of the two words or sets of words came closest to describing their present pain This was accomplished by asking patients to sort the cards into two piles labelled TOP and BOTTOM They were told that in some cases both words might describe their pain in which case they would be forced to opt for the word that came closest In some cases neither word might apply In which case they should choose the word which suggested to them the lesser amount of pain of the two words

The card sort was administered to 35 Caucasian women either during the experience of period pain or IUD related pain or just following the experience of such pain

Results The sample comprised 23 nulliparous women

Table III *Pain intensity ratings*

Word	Mean	Mode	S D	Frequency 1	2	3	4	5
Cutting	2 6	3	1 0	5	7	8	8	0
Unbearable	4 4	5	0 69	0	0	3	9	16
Tender	1 7	2	0 71	12	1[illegible]	4	0	0
Pulling	2 1	2	0 84	7	11	9	1	0
Pulsing	1 9	2	0 74	8	13	7	0	0
Stabbing	3 3	3	1 05	1	5	10	8	4
Shooting	3 35	3	1 1	2	3	11	7	5
Tearing	3 3	3	1 1	2	3	10	8	5
Pinching	2 0	1	0 96	10	9	7	2	
Dragging	[illegible] 3	2	0 95	5	11	8	4	
Annoying	2 0	1	0 96	10	9	7	2	
Cramping	2 7	3	1 0	3	8	10	6	1
Nagging	2 3	2	0 78	3	13	10	4	
Sharp	3 1	3	0 87	1	5	13	8	1
Throbbing	2 5	4	0 79	3	10	13	2	
Agonising	4 3	5	1 0		3	2	6	17
Wrenching	3 5	4	1 1	[illegible]	2	8	11	5
Exhausting	3 1	3	0 89	1	4	15	6	2
Sickening	3 1	3	1 0	2	4	13	6	3
Heavy	3 0	3	0 86	1	6	14	6	1
Intense	4 1	5	0 99	1		6	9	12
Pounding	3 1	3	1 0	3	3	11	9	2
Nauseating	3 2	4	1 1	1	7	7	9	4
Tearful	3 1	3	1 0	2	3	15	5	3
I	1 6	2	0 67	12	13	3		
	3 5	4	1 0	1	4	5	14	4
'	2 2	3	0 84	6	10	11	1	
	2 3	2	1 1	7	10	6	4	1
Aching	2 2	2	0 833	5	14	7	2	
Growing	2 6	2	1 0	4	9	9	5	1
Miserable	2 7	3	0 87	3	5	15	5	
Tiring	2 5	3	0 9[illegible]	5	6	14	3	
Tugging	2 3	2	0 81	4	13	9	2	
Prickling	1 7	2	0 85	12	14	1	1	

Table IV *10 pain questionnaire statements*

	Mean	S D	Range		Mean	S D	Range		Mean	S D	Range
Sensory											
1 Pulsing	1 9	0 7	([illegible])	Throbbing	2 5	0 79	(3)	Pounding	3 1	1 0	(4)
2 Dull	1 6	0 67	(2)	Aching	2 2	0 83	(3)	Heavy	3 0	0 86	(4)
3 Pulling	2 1	0 84	(3)	Cramping	2 7	0 1	(4)	Wrenching	3 5	1 1	(4)
4 Prickling	1 7	0 85	(4)	Boring	[illegible] 3	1 1	(4)	Stabbing	3 3	1 0	(4)
Affective											
5 Nagging	2 3	0 78	(3)	Sickening	3 1	0 1	(4)	Agonising	4 3	1 0	(3)
6 Slightly tiring				Tiring	2 5	0 9[illegible]	(3)	Exhausting	3 1	0 89	(4)
Temporal											
7 Brief				Every now and then				Constant			
Evaluative											
8 Annoying	2 0	0 9	(3)	Miserable	2 7	0 87	(3)	Unbearable	4 46	0 69	( )
9 Mild				Discomforting				Excruciating			
10 Slightly distressing				Distressing				Very distressing			

Table V *Menstrual questionnaire*

1	Backache	yes/no
2	General aching	yes/no
3	Take naps	yes/no
4	Accidents (e g cut finger break dish)	yes/no
5	Loss of appetite	yes/no
6	Leg ache	yes/no
7	Weakness	yes/no
8	Irritability	yes/no
9	Stay at home	yes/no
10	Unable to sleep	yes/no
11	Cramps	yes/no
12	Vomiting	yes/no
13	Avoid social activities	yes/no
14	Unable to concentrate	yes/no
15	Depression	yes/no
16	Headache	yes/no
17	Crying	yes/no
18	Stay in bed	yes/no
19	Lowered work/school performance	yes/no
20	Worn out	yes/no

and 17 who had had children Of the total of 35 25 were experiencing primary dysmenorrhoea and the remaining 10 IUD related pain The distribution of pain scores for each pain dimensions is presented in Table VI as well as the number of unreliable sorts for each pain dimension Inconsistent response patterns were assigned scores according to the guidelines set out by Shapiro (8) This involves making two assumptions One that once a set of responses have been accepted as reliable then the few inconsistencies that occur must be accepted as mistakes Two that the inconsistent pattern has been produced by only one mistake the other choices being free from error (Scoring instructions and pain manual available on request) Of the 35 patients 5 produced more than 2 inconsistent response patterns 8 produced 2 inconsistent response patterns 14 patients produced 1 inconsistent pattern and the responses of 6 patients were internally consistent

The relationship between card test scores and the self report of the behavioural effects of pain (symptom check list) were analysed by biserial correlations This was intended as a preliminary evaluation of the validity of the test The Kendall correlation coefficients between card sort scores and the occurrence of behavioural effects of pain are shown in Table VII It can be seen that the different card sort dimensions correlate with different symptoms both negatively and positively This suggests a low degree of overlap and duplicity between the card sort measures Thus a high score on dimension 1 was significantly correlated with the presence of backache accidents weakness and feeling worn out Dimension 2 was significantly correlated with accidents backache and leg ache A high score on this dimension correlated negatively with taking naps and being unable to sleep Headache was significantly correlated with dimension 3 Dimension 4 correlated significantly with loss of appetite and vomiting A high score on dimension 5—an affective dimension—was not positively associated with the presence of any symptom and negatively correlated with avoiding social activities and being unable to sleep Dimension 6 also from the affective category correlated positively with the presence of cramps vomiting and headache and was negatively associated with avoiding social activities The temporal dimension—no 7—correlated significantly with loss of appetite The evaluative dimensions were correlated with symptoms as follows Dimension 8 correlated positively with leg ache and backache and negatively with lowered work performance Vomiting was correlated with dimension 9 which was negatively correlated with loss of appetite cramps avoiding social activity and lowered work performance Dimension 10 also correlated with backache and headache

The correlation between symptoms and card sort scores for categories were also analysed It was found that the sensory total correlated significantly with backache being unable to concentrate and crying and negatively with general aching and taking naps The affective category score was positively correlated with the reporting of cramps vomiting and headache A high score on the temporal dimension was correlated with irritability The evaluative score correlated with backache legache vomiting headache and crying

Associations between pain scores on the card sort and type of pain were analysed by Chi square contingency

Table VI *Results of the card sort*

Pain questionnaire number	No of reliable *response* patterns	No of unreliable *response* patterns	Frequency of occurrence 1	2	3	4
1	29	6	6	11	9	9
2	29	6	7	11	9	8
3	30	5	2	21	7	5
4	27	8	2	8	11	14
5	24	11	16	14	3	2
6	33	2	11	7	10	7
7	31	4	1	15	5	14
8	31	4	14	8	9	4
9	35	0	12	16	11	6
10	31	4	17	7	4	6

Table VII *Biserial correlations between pain scores and reporting of menstrual symptoms*

Pain scores on each dimension	Menstrual symptom checklist									
	1	2	3	4	5	6	7	8	9	1[illegible]
1	30		− 08	36	06	28	35	08	16	−0[illegible]
2	18	− 20	− 21	23	− 12	27	− 13	− 04	− 10	−[illegible]
3	− 009	− 11	− 17	08	− 008	12	− 05	− 04	05	1[illegible]
4	− 01	− 15	05	24	338	− 09	09	07	17	[illegible]
5	− 09	− 25	− 22	09	− 08	07	− 21	02	− 09	−[illegible]
6	− 05	05	17	− 04	08	12	− 10	− 25	08	0[illegible]
7	12	− 03	03	02	21	04	− 15	12	03	
8	*18*	− *19*	− 15	*13*	− 09	27	08	0	− *01*	[illegible]
9	23	− 06	− 10	20	− 33*	28	− 14	− 19	01	−[illegible]
10	25	− 24	− 09	05	− 12	14	15	09	− 04	

$p<0\ 05$ $\quad p<0\ 01$

tables Only one significant association was found That was between dimension 7 and type of pain In other words type of pain—dysmenorrhoea or IUD related pain—was significantly associated with the score on the temporal dimension Women with dysmenorrhoea reported pain of a more continuous nature ($\chi^2=7\ 36$ df=3 $p<0\ 05$) This was also found in a self report survey (10)

The means for each pain category are presented in Table VIII A Pearson correlation analysis was computed and is presented in Table IX It can be seen that the dimensions correlate highest on the categories to which they had been allocated *a priori* Thus dimensions within the sensory category correlate most highly with the sensory category total The correlations between the sensory affective temporal and evaluative totals are given in Table X Although the correlation between both sensory and affective total scores with the evaluation total are significant the correlation coefficient is not high enough to suggest overlap

Table VIII *Summary statistics for pain categories*

	Mean	S D	Minimum	Maximum
Sensory	*10 6*	*2 5*	*6*	*15*
Affective	4 1	1 6	2	8
Temporal	2 9	0 98	1	4
Evaluative	6 6	2 8	3	12

DISCUSSION

Two existing approaches to pain measurement have been described which adhere to a multidimensional concept of pain The first consists of a questionnaire designed to evaluate three dimensions of pain—sensory affective and evaluative—presented by Melzack (11) The second consists of combinations of rating scales Both the rating scale approach—when used singly or in combination as in Johnson and Rice s study (12)—and the multiple item questionnaire (e g Melzack (11)) encounter methodological and procedural problems Given the general acceptance that the generic term pain subsumes a variety of pain dimensions the first difficulty with rating scales is the need to ensure that only one aspect of pain is being consistently responded to A second problem arises where the scale has been supplied with anchor points The assumption is that the various complex definitions

Table IX *Correlation between scores on pain dimensions with category totals*

	Card Sort 1	Card Sort 2	Card Sort 3	Card Sort 4	Card Sort 5	Card Sort 6	Card Sort 7
Sensory	708	6230	4323	7366	2470	0919	0 3530*
Affective	− 07_5	2728	3233	1405	7741	8697	0 0614
Temporal	2599	3 84	− *1027*	*4729*	*0517*	*0501*	1 00*
Evaluative	1723	3 60	830	3416	4_50	3537	0 1500

$p<0\ 05$ $\quad p<0\ 01$

11	12	13	14	15	16	17	18	19	20
09	07	17	11	12	08	10	− 07	− 002	3 0
005	− 13	− 11	− 11	− 19	− 26	06	− 16	− 12	− 08
01	− 01	03	21	− 01	45	17	− 19	− 05	03
26	21	07	01	11	− 005	− 15	01	− 08	12
003	− 04	− 4	− 25	− 24	− 07	− 17	− 11	− 31	− 21
34 *	29	− 29	− 08	− 17	33	− 18	11	− 20	04
06	09	005	− 06	005	− 12	− 18	09	− 03	− 15
12	10	04	− 07	14	08	0	− 03	− 27	13
14	21	− 23	− 20	− 09	07	07		− 33	− 06
04	03	− 04	− 01	13	21	13	10	− 16	08

constitute a properly ordered scale In fact the subject may not be able to discriminate reliably between the points and some of them may not be on the same dimension In the multiple item questionnaire procedure the subject is required to give his response to each of a number of questions Each response is quantified and a total score computed This approach also encounters problems in the assessment of pain intensity This is largely due to the problems of establishing the degree to which each item contributes to the total pain scores as distinct to the amount of variance for each item that can be ascribed to error or to factors specific to that item only

Both approaches have procedural difficulties The single rating scale may be easy to administer but may not reliably reflect the behaviour under investigation When more than one scale is used there may be problems in ensuring that the ratings are understood and used in a consistent manner The questionnaire approach may prove too lengthy for ill patients and so yield unreliable measures owing to the complexity of the format

In view of the limitations of these two approaches to pain a third method was developed which we have presented in this paper The results of the survey carried out in Stage I indicated high consensus over the words used to describe primary dysmenorrhoea and IUD related pain—with few differences between them This allowed a *standard* card sort to be developed and used in the assessment of these two pains Owing to its pair comparison format the card sort includes an internal consistency check Only five of the patients produced more than two inconsistent response patterns Some response patterns were more likely to give rise to unreliable response patterns e g (dimensions 4 and 5) These could be excluded from further assessments With these dimensions excluded the majority of patients produced no more than one inconsistent response which indicates high reliability for the test as a whole

A preliminary evaluation of the validity of the card sort consisted of comparing their scores with the self reported occurrence of pain symptoms No consistent picture emerged from this A large number of the correlations were negative—indicating that the occurrence of pain on the card sort was

...rd ...rt 8	Card Sort 9	Card Sort 10
358	4521	4163
165	5350	4366
5 9	1176	1076
557	7942	8973

Table X *Correlation between pain category scores*

	Sensory	Affective	Temporal	Evaluative
Sensory		07	26	47
Affective			07	30
Temporal				04
Evaluative				

$p<0\ 01$

not related to the reporting of symptoms It is felt that no definite conclusions can be drawn from this It seems possible that low correlation may have been due to the operation of response sets on the self report measure which did not influence the card sort to the same degree Thus some patients with pain may have been disinclined to report pain symptoms Face validity of the test can be drawn from its ease of administration and the informal comments made by women during the interview Many patients expressed satisfaction at being provided with an opportunity to convey the exact nature of their pain

The advantages offered by this assessment approach warrant consideration The method provides the patient with a controlled and reproducible method of assessing the severity of the pain In this way it offers the clinician a relatively direct and uncontaminated communication by the patient of the intensity and the nature of the pain Moreover it furnishes a clear indication of the course of the pain experience over a long period of time Its adherence to a multidimensional concept of pain permits the comparison of the relative intensities of different symptoms/pain dimensions This makes possible the comparison of the intensity of distress of different individuals

The method of pair comparisons offer a number of methodological advantages

1) it requires a number of judgements for each dimension thus increasing the reliability of each assessment

2) each judgement is likely to be reliable for it requires a choice between only two statements

3) the paired comparison format provides an internal reliability test Clearly the data collected by the pain questionnaire would be useless for further examination if it were shown to be unreliable or influenced by position set There are 4 inconsistent response patterns If patients are responding consistently and there is consensus over the meanings of the words employed these patterns will not be produced If the patient is responding randomly then all 8 different response patterns would be produced in equal proportion A statistical test (Chi square) can be used to determine the significance of the distribution of the response patterns This test can be applied to any occasion of testing or to any triad after a number of assessments

The clinical use of this assessment method appears to hold some promise The assessment is easy to administer and minimises interviewer bias Th test has low visibility for the patient—which shoul serve to minimise the possibility of faking of r sponses The administration takes very littl time—in the present study with 30 cards the aver age sort time was 3 min Scoring took less than l min to complete Once completed the clinician is in a position to tell at a glance the severity of the pa across a number of relevant dimensions For exa ple a number of patients scored at maximum seve ity on the sensory dimensions but at minimal sever ity levels on the evaluative dimensions The patter of scores may influence treatment interventio Thus medication may reduce the severity of sensory scores while reassurance and informatio may be sufficient in many cases to reduce the in tensity of affective and evaluative scores It appear that the present assessment format provides an op portunity to assess the independent response of pain dimensions to different treatment regimes bo psychological and pharmacological

In a study investigating the effects of ethnic ori and pain Johnson & Rice (12) drew a distincti between the sensory input and the reaction to (distress) Ethnic origin appeared only to affect d tress ratings Thus another potential advanta concerns the utilisation of this pain assessment other cultures The content of the card sort is r limited to any one culture as it is supplied on t basis of preliminary field work Similarly t method is not limited in use to the pains und investigation Once again on the basis of prelin nary field work it would be possible to establish t content of the card sort for other clinical pains

In view of these findings and the potent advantages offered by this assessment procedure is felt that there is sufficient indication for its util to support a more extensive evaluation This wou require the assessment of pain over a period of ti in order to establish the efficacy of treatment Th card sort method would be compared with oth pain indices These would include the behaviour effects of pain—such as pill taking staying off wo etc —as well as measuring the subjective aspects pain by alternative methods—such as rating scale and self monitoring the occurrence Such a stud could provide clear indications as to the validity o the measurement approach A more extensiv evaluation of this card sort method investiga methods of treating primary dysmenorrhoea a IUD related pain is currently being undertaken

REFERENCES

1 Huskisson E C Measurement of pain Lancet *2* 1127 1974
2 Agnew D C & Merskey H Words of chronic pain Pain 2 73–81 1976
3 Davidson P O & Neufeld W J Response to pain and stress multivariate analysis J Psychosom Res *18* 25 1974
4 Melzack R The puzzle of pain Penguin London 1973
5 Scott J & Huskisson E C Graphic representation of pain Pain *2* 175 1976
6 Bergsjo P Jenssen H & Zellar O D Dysmenorrhoea in industrial workers Acta Obstet Gynecol Scand *54* 355 1975
7 Population Reports Series B No 2 January 1975
8 Shapiro M B The Personal Questionnaire A method of measuring changes in the symptoms of an individual psychiatric patient Unpublished abbreviated manual Institute of Psychiatry London 1961
9 Melzack R & Torgerson W S On the language of pain Anaesthesiology *74* 50 1971
10 Reading A E & Newton J R A comparison of intrauterine device related pain and primary dysmenorrhoea Pain *3* 265 1977
11 Melzack R The McGill Pain Questionnaire Major Properties and Scoring Methods Pain *1* 277 1975
12 Johnson J E & Rice V H Sensory and distress components of pain implication for the study of clinical pain Nursing Research *23* 03 1974

Submitted for publication Feb 22 1978

John R Newton
Department of Obstetrics and Gynaecology
King s College Hospital Medical School
Denmark Hill
London SE 5
England

BOOK REVIEWS

Amniotic Fluid 2nd edition completely revised by *D V I Fairweather* and *T K A B Eskes* Elsevier/North Holland Biomedical Press Amsterdam Oxford New York 1978 (ISBN 90 219 2111 1) 455 pages US dollars 78 25

The first edition of this book was published in 1973 and was very much appreciated All chapters have now been updated and revised and four new chapters concerning chemical examination of amniotic fluid have been added The authors of the different chapters are well known specialists within their fields The editors have done an excellent work co ordinating the various chapters The book is recommended for all departmental libraries of obstetrics and gynecology

I S

Ultrasound in Obstetrics and Gynecology by *Lothar Popp* and *Russel J Thomsen* Hemisphere Publishing Corporation McGraw Hill Book Company New York 1978 (ISBN 0-07 050507 1) DM 40 70

This textbook provides facts of obstetrical and gynecological ultrasound on a level suited for the clinician or the student The authors have produced a logical guide to the principles of ultrasound which leads to an understanding of the actual methods of performing the ultrasonic examination and the basis of interpreting the resulting ultrasonic scans

The book contains ultrasonic pictures taken from the extensive clincal experience of the authors Pictures of scans that clearly and typically illustrate the principles of ultrasound as developed through the text have been used

This book is highly recommended as a comprehensive survey and useful introduction to the field of obstetric ultrasound

I J

Surveillance for the prevention and control of health hazards due to antibiotic resistant enterobacteria Report of a WHO Meeting *World Health Organization Technical Report Series* 1978 No 624 (ISBN 92 4 120624 1) 55 pages Sw Fr 6

The uncontrolled and excessive use of antiobiotics in man and animals has lead to a disturbing increase in drug resistance on the part of pathogenic organisms and is diminishing the effectiveness of life saving drugs There is therefore a need for more rational and coordinated administration of antibiotics and for strict measures against their abuse

This report outlines the factors involved in the emergence and spread of antibiotic resistance in enterobacteria as well as the ways of controlling such resistance Appropriate laboratory methods and the collection and processing of data are described

The report lists areas requiring further research including the development of simpler and more rapid susceptibility tests methods for the analysis and interpretation of the results of such tests studies of the clinical and epidemiological relevance of resistant bacteria and the environment and the development of effective methods for the control of resistant microorganisms of human and animal origin

Clinics in obstetrics and gynecology volume 5 no 3 December 1978 *Gynaecological Surgery* 747 p Guest editors *David H Lees* and *Albert Singer* W B Saunders Company Ltd London 1978 Pound sterling 8 25

The current status of gynecological surgery is described in 14 chapters written by important specialists in the different fields Thus abdominal hysterectomy is described by S Joel Cohen Surgery of vulval carcinoma by Stanley Way Microsurgery in infertility by Robert Winston etc

The book is recommended to all colleagues specializing in gynecologic surgery

I S

Obstetrics & Gynaecology by *R W Taylor* and *M G Brush* Baillière Tindall London 1978 (ISBN 0 70 0 0664 0)

During the past decade complexe techniques in obstetrics and gynecology have been introduced Many of us have changed our ideas about the material which an undergraduate student should be presented with The student s demand on the quality of his textbook has changed too He needs a compact book which will give him an overview of the subject and which can be read easily at an early stage in the course of obstetrics and gynecology thereby enabling the student to gain maximum benefit from the teaching in the clinical situations

The authors of Obstetrics & Gynaecology have been successful in their endeavour to create a comprehensive text fulfilling the above requirements

Subjects such as sexual relationships family planning and physiological problems have been included

I J

Research in human reproduction Strengthening in resources in developing countries Report of a WHO Study Group *World Health Organization Technical Report Series* 1978 No 627 (ISBN 92 4 120627 6) 16 pages Sw Fr 4

The contribution that research on health problems can make to general development in the less industrialized countries is now widely recognized In the field of human reproduction and family planning the many problems requiring investigation have stimulated the growth of resources for research but little concrete advice is available on how to set about strengthening these resources in the developing countries

For a number of years the WHO special program of research development and training in human reproduction has worked with governments and institutions in the developing countries to build up their research resources in the field In July 1978 the study group was convened to analyze actual experiences This short report sums up the general principles that emerged from the groups close study of the successes and obstacles encountered by each of the institutions The points outlined in the report should be helpful to scientists trying to build up their own facilities to those responsible for research administration and support at the national level and to other organizations and agencies that promote and support research

Acta Obstet Gynecol Scand 58 115–120 1979

MULTICHANNEL INTRAUTERINE PRESSURE RECORDING BY MEANS OF MICROTRANSDUCERS

Ulf Ulmsten and Karl Erik Andersson

From the Department of Obstetrics and Gynecology University Hospital of Malmo Sweden and the Department of Clinical Pharmacology Institute of Pharmacology University of Århus Århus Denmark

Abstract Intrauterine pressures (IUP) were recorded simultaneously at the fundus the isthmus and cervix uteri by means of three micro-transducers (in 20 healthy non pregnant women and in 5 patients with severe primary dysmenorrhoea) Recordings were performed during the first 3 days of the menstrual cycle Both incoordinate and coordinated myometrial activity was recognized When coordination was present the contraction wave as a rule started in fundus and was propagated towards the isthmus and cervix Pinching and/or palpation of the cervix elicited retrograde contractions i e the contraction wave started in the cervix and moved towards the fundus It was frequently observed that during vigorous contractions of the fundus the pressure increase in the isthmus was small in some cases even a decrease in pressure occurred in this region The pressure recording technique functioned perfectly during all recordings and seems to facilitate detailed studies of myometrial activity in the non pregnant uterus

Intrauterine pressure (IUP) recordings as a measure of myometrial activity in the non pregnant uterus have so far been performed mainly by the use of fluid filled open ended or balloon catheters These catheter techniques have several biotechnical disadvantages (for discussions see 9 8 16) Recently micro-transducers have been introduced for recording intraluminal pressures in the urinary tract (2 3) this technique seems also to be superior to previously used methods for intrauterine pressure recordings in the non pregnant uterus (19)

The present study was undertaken to record simultaneously the IUP in three different parts of the non pregnant human uterus Thus the IUP in the fundus isthmus and cervix uteri were recorded with the aid of micro-transducers The recordings were performed at the beginning of menstruation as previous investigators have shown the occurrence of labour like uterine contractions during this period (13 15) These contractions seem to be propagated from the fundus to the cervix uteri (5 6) It was thought that with the present technique it would be possible to elucidate whether myometrial activity varied in different parts of the uterus and if coordination of activity was recognizable

METHODS

Subjects

Twenty healthy women and 5 patients suffering from severe primary dysmenorrhoea volunteered for the study Their mean age was 31 years (range 24–40 years) Before the investigation they were carefully informed of its purpose

The recordings were performed on days 1 to 3 of the menstrual cycle Two of the women had IUDs (Cu T) and none were on drug therapy when the recordings were performed

Pressure recording technique

The recording catheter (Fig 1) consisted of a teflon catheter which enclosed three micro-transducers (Millar Instruments Houston Texas) 3 cm apart Each pressure sensing section of the catheter had an active pressure sensor area of 0 75 mm² This allowed recording of the IUP from well-defined positions Due to its compliance the frequency response of the microtransducer is more than 2000 Hz assuring a high sensitivity of the recording system

After amplifying the pressure signals from the transducers were registered by an Omniscriber WTR 281 (Watanabe Japan) or by an ink jet recorder (Mingograph 81 Siemens Elema Stockholm Sweden) Before and after every recording the equipment was calibrated in a special calibrator allowing static dynamic and electronic calibration of the instrument (4)

Experimental procedure

Before the recordings all patients had a routine gynecological examination and an ultrasound scanning of the pelvic organs This provided information on the shape and size of the uterine cavity The size of the uterine cavity was also estimated by sounding

The recording catheter was introduced transcervically into the uterine cavity It was kept in position by means of sterile compresses surrounding the catheter in the vagina The recording sections or micro-transducers of the cathe

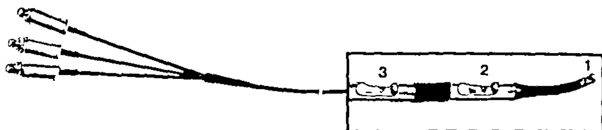


Fig 1 The pressure recording catheter Within the frame the distal part of the catheter is shown in larger scale The three micro-transducers are located 3 cm part The connection plugs to the amplifier are seen at the proximal end of the catheter

ter were placed as follows no 1 (located at the end of the catheter see Fig 1) in the uterine fundus no 2 in the isthmic part of the uterine cavity and no 3 in the mid part of the cervical canal

All recordings were performed with the subjects in the supine position and with an empty bladder No anaesthesia was used The time of recording varied be tween 80 and 240 min

Interpretation of the records definitions

The *resting pressure* is defined as the lowest pressure between two consecutive uterine contractions *Contraction pressure amplitude* is the difference between resting and the peak pressure of the contractions *...dinated or propagated contractions* are first recorded ...one micro-transducer and after some time lag also by ...e adjacent transducers (Figs 3 and 5) *Incoordinated or asynchronous contractions* are recorded by the different micro-transducers without any time relation They have often different frequencies at the different regions (Fig 2)

RESULTS

In all investigations the calibrations before and after the recordings were in complete accordance No subject experienced any discomfort caused by the recording catheter and no side effects were observed during or after the studies

The absolute values of IUP varied between the women but also between the different uterine sites in the same woman In healthy subjects the resting pressure at the uterine fundus averaged 18 mmHg (range 8–52 mmHg) within the isthmic area 13 mmHg (range 9–46 mmHg) and in the cervical canal the resting pressure as a rule showed small variations averaging 18 mmHg

The highest contraction pressure amplitude was found at the uterine fundus where it averaged 86 mmHg (range 36–156 mmHg) In the isthmic part of the uterine cavity the mean pressure amplitude was 71 mmHg (21–111 mmHg) In the cervical canal the contraction complexes usually had a small amplitude only occasionally exceeding 40 mmHg

In the two females with IUD the measured parameters did not differ from those found in the other subjects However in patients suffering from dysmenorrhoea both the resting pressure and con-

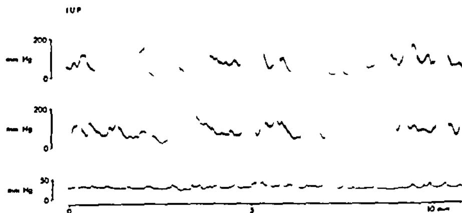


Fig 2 Intrauterine pressure recording from a patient with severe primary dysmenorrhoea Upper tracing fundus uteri middle tracing isthmus uteri lower tracing cervix uteri The uterine activity is characterized by asynchronous contractions high resting pressure and high contraction pressure amplitudes

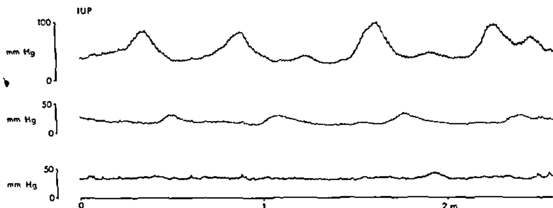


Fig 3 Intrauterine pressure recording from one of the healthy subjects Upper tracing fundus uteri middle tracing isthmus uteri lower tracing cervical canal The myometrial contractions start at the fundus and propagate towards the cervix i e in an antegrade direction

traction pressure amplitudes although variable were considerably higher than in the healthy subjects and uterine activity was often characterized by asynchronous contractions (Fig 2)

Coordinated myometrial activity was not a consistent finding but it was observed in all subjects Three types of coordination could be recognized

(a) Antegrade myometrial activity i e the con

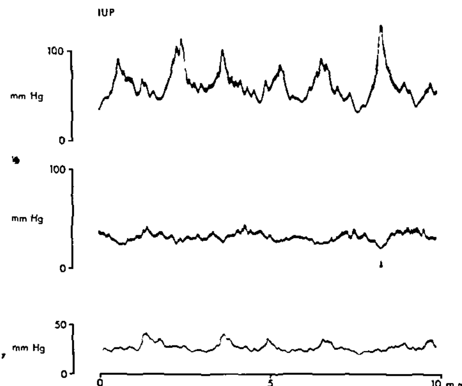


Fig 4 Intrauterine pressure recording from one of the healthy subjects Relatively strong contractions are seen within the fundus (upper tracing) Simultaneously there is occasionally a decrease in the pressure within the isthmus (middle tracing arrow)

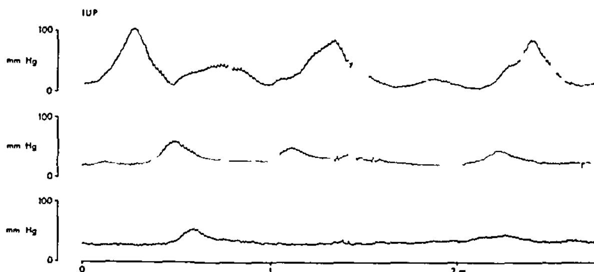


Fig 5 Intrauterine pressure recording showing a change in direction of contraction waves Upper tracing fundus uteri middle tracing isthmus uteri lower tracing cervix uteri In the left part of the figure is seen antegrade propagation which is spontaneously changed to retrograde propagation

tractions were initiated in the fundus and propagated towards the isthmus and the cervix (Fig 3)

(b) Strong contractions which started in the fundus and were accompanied by a moderate increase or a decrease of the pressure in the isthmus and the cervix (Fig 4)

(c) Retrograde activity i e the myometrial activity started in the cervix and was propagated towards the fundus (Fig 5) The last type of activity was seldom seen spontaneously but could be elicited by palpation or pinching of the cervix

In some women pressure recordings were also

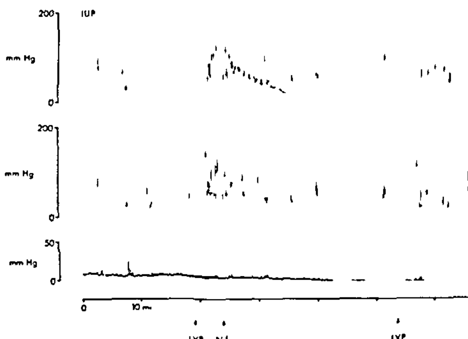


Fig 6 Intrauterine pressure recording showing the stimulating effects of lysine vasopressin (LVP) on the intrauterine pressures within the fundus (upper tracing) and isthmus uteri (middle tracing) The effects of vasopressin are counteracted by nifedipine (Nif) 30 mg orally No effects are seen on the pressures within the cervix (lower tracing)

performed immediately after ovulation as judged from basal temperature measurements and vaginal smears In these retrograde contractions was easily elicited by touching the cervix

In a few subjects the spontaneous myometrial activity was increased (Fig 6) by intravenous injection of lysine vasopressin 0 2 mU Both spontaneous and vasopressin induced myometrial activity was reduced by the calcium antagonist nifedipine (17) The recordings within the fundus and isthmus uteri were very similar in these cases (Fig 6)

DISCUSSION

It is generally accepted that the IUP reflects myometrial activity but so far no ideal method has been devised for its direct translation (9 1) Because the use of various non standardized techniques the results of different IUP recordings have been difficult to compare (8) Even if the IUP technique used in this study is regarded as adequate artefacts may not be completely excluded Dependent upon the position of the microtransducer i e the sensor area facing the uterine wall or the inside of the uterine cavity—differences in resting pressure and contraction amplitudes might be recorded (19) To avoid these variations all measurements were made with the micro-transducers facing the upper uterine wall Because the uterine cavity is not a true cavity but a mere slit close contact with the uterine wall could be obtained by all the microtransducers That this actually occurred is supported by the fact that marked arterial pulsations could be recorded by all the recording sections Because of this contact the pressure transducers were most probably directly influenced by contractions of the myometrium

Very few reports of recordings of myometrial activity simultaneously at different parts of the uterus have been presented (see e g 5 10 14) In accordance with previous results obtained by other recording techniques the present investigation showed that coordinated myometrial activity occurred during menstrual bleeding The appearance of retrograde myometrial activity most pronounced during midcycle is also in accordance with the resports of Behrman et al (5) It is interesting to note that retrograde contraction waves could be elicited by palpation or pinching of the cervix It might be that such retrograde contractions are of importance for the transport of seminal fluid but further investigations are necessary to testify such a speculation

It was often noted that simultaneously with vigorous contractions of the uterine fundus there was no increase but a decrease of the pressure within the isthmical and cervical parts of the uterus (Fig 4) From a hydrodynamic point of view this is a rational response of the uterus to facilitate emptying the cavity of menstrual blood A high pressure in the cervical and isthmic regions would of course counteract such an emptying procedure

Coordinated myometrial activity was often interrupted by incoordinated contractions The occurrence of spontaneous changes in uterine activity without correlation to known influences has also been stressed by e g Hendricks (12) Most reasonably this non synchronized myometrial activity is due to local myometrial contractions which because of the shape of the non pregnant uterine cavity are directly recorded by the microtransducers This suggestion is supported by the findings of Borell et al (7) They demonstrated by means of hysterography the occurrence of strictly localised myometrial contractions in the non pregnant uterus

Asynchronous contractions high resting pressure and high contraction pressure amplitudes characterized the uterine activity of the women with primary dysmenorrhoea These findings are in accordance with those reported by other investigators using other techniques of recording (18 11)

Most investigators have stressed the difficulties in characterizing the coordinated activity of the non-pregnant uterus during prolonged recording sessions It has been suggested that as small recording devices as possible should be used in order not to transform the uterine slit into a real cavity If this happens the sum of all local activities will be recorded The present technique seems to be suitable for recording of myometrial activity in different parts of the uterus It might be useful for studies of the myometrial activity in patients with dysmenorrhoea potential retrograde menstruation and unexplained causes of sterility

REFERENCES

1 Anzén B Hysterometry—a method for in vivo determination of pharmacologic effect on the myometrium Thesis Karolinska Institutet Stockholm 1977

2 Asmussen M & Ulmsten U Simultaneous urethro-cystometry and urethral pressure profile measurement with a new technique Acta Obstet Gynecol Scand *54* 385 1975
3 Asmussen M & Ulmsten U A new technique for measurements of the urethral pressure profile Acta Obstet Gynecol Scand *55* 167 1976
4 Asmussen M Lindström K & Ulmsten U A catheter manometer calibrator—a new clinical instrument Biomed Eng *10* 175 1975
5 Behrman S J Archie J T & O'Brien O P Myometrial activity and the IUCD II Propagation waves Am J Obstet Gynecol *104* 123 1969
6 Bengtsson L P Hormonal effects on human myometrial activity *In* Vitamins and Hormones vol 31 257 1073 Academic Press New York and London
7 Borell U Fernstrom I & Ohlson L Membrane like structures in the uterine cavity A hysterographic study Acta Obstet Gynecol Scand *49* 185 1970
8 Braaksma J T Janssens J Eskes T K A B & Hein P R Accurate pressure recording in the nonpregnant uterus A comparison of open and closed tip catheter Eur J Obstet Gynecol *6* 195 1971
9 Csapo A The diagnostic significance of the intrauterine pressure Obstet Gynecol Surv *5* 403 1970
10 Csapo A I & Pinto-Dantas C R The cyclic activity of the nonpregnant human uterus A new method for recording intrauterine pressure Fertil Steril 34 1966
Filler W W & Hall W C Dysmenorrhea and its therapy A uterine contractility study Am J Obstet Gynecol *106* 104 1970
12 Hendricks C H In vivo studies of motility patterns in the nonpregnant human uterus Obstet Gynecol *25* 471 1965
13 Hendricks C H Inherent motility patterns and response characteristics of the non pregnant human uterus Am J Obstet Gynecol 96 824 1966
14 Martinez-Gaudio M Yoshida T & Bengtsson L P Propagated and nonpropagated myometrial contractions in normal menstrual cycles Obstet Gynecol *115* 107 1973
15 Moawad A H & Bengtsson L P In vivo studies of the motility patterns of the non pregnant human uterus I The normal menstrual cycle Am J Obstet Gynecol *98* 1057 1967
16 Ulmsten U Studies on ureteral function in women Thesis University of Lund 1974
17 Ulmsten U Andersson K E & Forman A Relaxing effects of nifedipine on non pregnant human uterus *in vitro* and *in vivo* In manuscript 1977
18 Woodbury R A Torpin R Child G P Watson H & Jarboe M Myometrial physiology and its relation to pelvic pain J Am Med Ass *134* 104 1970
19 Åkerlund M Bengtsson L P & Ulmsten U Recording of myometrial activity in the nonpregnant uterus by a micro-transducer catheter In press

Submitted for publication Oct 26 1977

Ulf Ulmsten
Department of Obstetrics and Gynecology
University Hospital
S 21401 Malmö
Sweden

Acta Obstet Gynecol Scand 58 121–122 1979

SHORT COMMUNICATION

THE EFFECT OF INDOMETHACIN ON THE INSTILLATION ABORTION INTERVAL IN RIVANOL INDUCED MID TRIMESTER ABORTION

Anders Olund

From the Department of Obstetrics and Gynecology Karolinska institutet Huddinge University Hospital Huddinge Sweden

Extra amniotic instillation of Rivanol for the induction of mid trimester abortion is a safe and effective method and its clinical value has been described in several reports (for ref see (5))

The mechanism by which Rivanol induces abortion is however still obscure

It has been proposed that hypertonic saline induces abortion by stimulating the release of endogenous $PGF_{2}\alpha$ (1) The fact that prostaglandin synthetase inhibitors prolong the induction abortion interval in saline induced abortion lends further support to this theory (4) The purpose of the present study was to examine possible effects of indomethacin a strong prostaglandin synthetase inhibitor on mid trimester abortion induced by Rivanol

MATERIAL AND METHODS

Twenty women were included in the indomethacin group and 55 women in a control group who were admitted to the hospital for legal abortion during the period 1975–1977 The mean gestational age (±1 S D) was 16 1±2 7 weeks in the indomethacin group and 15 6±2 1 weeks in the control group

In all cases the abortion was induced by extra amniotic instillation of Rivanol A Foley balloon catheter no 20 was introduced into the extra ovular space via the cervical canal The tip of the catheter was placed just inside the internal os of the cervix and the balloon was filled with 30 ml of physiological saline A 0 1% solution of Rivanol was then slowly instilled 10 ml per gestational week but never more than 150 ml after which the catheter was tied off at its lower end The catheter was left in place for 24 hour or expelled with the fetus if the patient aborted earlier If the abortion had not started by the following morning an intravenous infusion of oxytocin 70 IU in 1000 ml of 5 5% glucose was commenced This infusion was repeated every 12th hour until abortion occurred

The indomethacin group were treated with 50 mg indomethacin (indomee®) orally every six hours for a maximum of seven doses with the first dose just before the instillation of Rivanol A further instillation of Rivanol was performed if the patient had not aborted by 72 hours

RESULTS

The mean induction abortion interval was 32 3 hours (range 13 0–96 0) in the control group and 46 9 hours (range 19 7–91 0) in the indomethacin group The cumulative abortion rate for the control group versus the indomethacin treated patients is shown in Fig 1 All patients requiring a second instillation aborted within a further 24 hours

Indomethacin significantly prolonged the induction abortion interval ($p<0\ 005$ Student s t test)

Excessive blood loss and endometritis were equally common in the two groups (control group 10 9% and indomethacin group 10%)

DISCUSSION

Although Rivanol has been used to induce abortion for more than 20 years the underlying mechanism is still obscure An oxytoxic effect of related acridin dyes has been reported (2) but this does not fit in with the rather long initial lag time before the appearance of significant uterine contractions as reported by Martin et al (3) Gustavii et al (1) have shown endogenous release of prostaglandin after instillation of hypertonic saline for the induction of abortion Waltman and collaborators (4) administered indomethacin a strong inhibitor of prostaglandin synthesis to patients undergoing

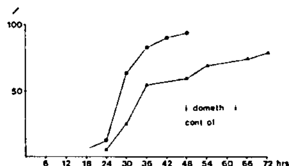


Fig 1 Percentage of patients aborting per six hours unit of time

saline induced mid trimester abortion The result was a significantly prolonged instillation abortion interval supporting a prostaglandin mediated mechanism behind the abortifacient effect of hypertonic saline

Martin et al (3) postulated a similar mechanism for Rivanol as for saline The high incidence of gastrointestinal side effects with Rivanol (5) lends further support to this theory The results of the present study with a significant prolongation of the induction abortion interval after the administration of indomethacin strongly suggest that the effect of Rivanol is mediated through stimulation of the endogenous production of prostaglandins

REFERENCES

1 Gustavii B & Gréen K Release of prostaglandin $F_{2\alpha}$ following injection of hypertonic saline for therapeutic abortion A preliminary study Am J Obstet Gynecol *114* 1099 1972
2 Lewis B V Pybus A & Stillwell J H The oxytocic effect of acridin dyes and their use in terminating mid trimester pregnancy J Obstet Gynaecol Br Comm *78* 838 1971
3 Martin J N Bygdeman M Leader A & Wiqvist N Early second trimester abortion by the extraamniotic instillation of Rivanol solution and a single $PGF_{2\alpha}$ dose Contraception *11* 573 1975
4 Waltman R Tricomi V & Palay A Aspirin and indomethacin Effect on instillation/abortion time of mid trimester hypertonic saline induced abortion Prostaglandins *3* 47 1973
5 Ölund A R & Larsson B Comparison of extraamniotic instillation of Rivanol and $PGF_{2\alpha}$ either separately or in combination followed by oxytocin for second trimester abortion Acta Obstet Gynecol Scand *57* 333 1978

Submitted for publication Sept 8 1977

Anders Ölund M D
Department of Obstetrics and Gynecology
Huddinge Hospital
S-141 86 Huddinge
Sweden

Acta Obstet Gynecol Scand 58 123 1979

LETTER TO THE EDITOR

Dear Sir

The issue of a possible relationship between cancer of the endometrium and exposure to exogenous estrogens has been intensively debated especially since the report of Ziel and Finkle in 1975 Several retrospective studies seem to reveal a higher than normal risk for developing endometrial cancer among women on an estrogen regimen In Sweden the post menopausal use of conjugated estrogens has become more and more popular from 1974 and onwards although lately it has stagnated somewhat as a consequence of the above mentioned alarming reports from the United States and Great Britain The need for a survey of the extent of estrogen medication among the female population of postmenopausal age as well as among patients with endometrial carcinoma has brought about the following investigation of which we would like to present part of the results immediately thus anticipating the future more detailed article

Material and Method The total previous use of synthetic and conjugated estrogens singly or combined with progesterone or androgens was thoroughly penetrated in the 622 new cases of adenocarcinoma of the endometrium treated at Radiumhemmet 1974-77 and also in a control group of 1428 women matched for age but otherwise randomly selected among the female population of Stockholm and its surroundings The information taken from case reports was double checked by personal interviews and found to be reliable The controls answered a written enquiry which was returned and adequately answered by 80 per cent of the 1866 contacted women

Results The trend of an increasing use of conjugated estrogens (principally not combined with progesterone) was obvious in the control group and even more so in the cancer group

The difference was most pronounced in 1977 and concerned mainly the use of conjugated estrogens Table I

A closer penetration showed that short term use (less than 3 years) was as common in the control group as in the cancer group while long term treatment (3 6 years of medication) was more than five times as common among the cancer patients 1976 1977 Table II

Comment We would like to point out that a connection between long term estrogen use and endometrial adenocarcinoma no doubt exists also in our Swedish material Of course mere analysis of the data presented here cannot clarify the nature of such a connection It still cannot be proved that estrogen medication is of importance for the genesis of endometrial cancer However considering these results we believe that long term treatment with estrogens alone should only be prescribed on distinct medical indications

Stockholm September 16 1978

Anders Öbrink *Görel Bunne*
Johan Collen *Bengt Tjernberg*

Department of Gynecologic Oncology
Radiumhemmet
S-104 01 Stockholm Sweden

Table I *Distribution by study group and year of women (%) with more than 6 months of estrogen medication (synthetic and/or conjugated contraceptives excluded)*

	1974	1975	1976	1977
Cases (50-69 yrs)	8 1	17 0	23 0	35 6
Controls (50-69 yrs)	6 6	8 6	12 6	16 7
Sign of difference		p<0 05	p<0 01	p<0 001

Table II *Estrogen use (as percentage) among women aged 50-69*

	Duration 6 36 months			
	1974	1975	1976	1977
Cases	4 7	9 1	5 7	10 6
Controls	3 9	7 3	9 9	11 1
	Duration 37 72 months			
	1974	1975	1976	1977
Cases	2 3	4 5	11 5	20 2
Controls	1 6	1 3	2 5	3 5
Sign of difference			p<0 01	p<0 001

Acta Obstet Gynecol Scand 58 125–126 1979

LETTER TO THE EDITOR

Sir

Ovarian carcinoma is the fourth most frequent cause of death from cancer among women Most patients present large pelvic tumors on admission In Denmark the standard regimen in the advanced cases (F I G O stage III and IV) is primary surgery with biopsy and extensive resection of tumor masses followed by chemotherapy with dihydroxybusulfan (Treosulfan) and in some cases by radiotherapy However the results are generally discouraging and the therapy is still under discussion

It is essential first to evaluate the malignancy of the tumor and to classify it Then the therapy can be decided and it should only in some cases be primary surgery (1) The need of a simple and safe bioptic technique which can permit a histological classification is evident

Vaginal fine needle aspiration biopsy has been used in Scandinavia since 1965 with good results and very few complications but generally it can only permit a cytological diagnosis because of the limited bioptic material (5 6) Large needle aspiration techniques have been widely used for percutaneous liver biopsy since 1939 and for percutaneous kidney biopsy since 1951 using the needles of Iversen–Roholm and Menghini or modifications (3 4 7) These techniques are generally considered as safe and suitable for histological biopsy of the liver and kidney To my knowledge vaginal large needle aspiration biopsy has not been used in women presenting large pelvic tumors indicating advanced ovarian carcinoma In the following a new technique for vaginal fine needle and large needle aspiration biopsy in advanced pelvic tumors is reported

The technique consists of two bioptic procedures which are performed in the same seance without anaesthesia The instruments are seen in Fig 1 For fine needle biopsy I use a stiff needle (diameter 0 8 mm) which can be inserted without guidance For the large needle biopsy I use Brun s modification of the Iversen–Roholm needle (length 150 mm outer diameter 2 0 mm inner diameter 1 7 mm sharp right angled tip without notches) (2) Prior to the biopsy the bladder is emptied and the vagina is cleaned with an antiseptic solution

The technique

I *Vaginal fine needle aspiration biopsy*

Supported by the index finger the needle is inserted via the vagina into the tumor preferably in the pelvic axis The tumor should be palpated directly with no suspicion of visceral interposition Suction is applied with the Franzen syringe and the needle is moved in and out of the tumor It is important to notice the structure and mechanical properties of the tumor during the operation The needle is withdrawn and suction released when the tip is just below the vaginal mucosa The cell material in the needle is ejected onto microscope slides for later cytological investigation If fluid is obtained in the syringe it is examinated visually and prepared for later cytological investigation too The next procedure should not be performed if the fine needle aspirate by visual examination of the content of the syringe is found to be fluid from a cyst blood from a larger vessel urine intestinal content or pus from an abscess If no or just minimal fluid is obtained in the syringe and the tumor concluded to be solid the next procedure can be performed immediately

II *Vaginal large-needle aspiration biopsy*

The trocar is inserted through the vaginal puncture canal just made preferably in the pelvic axis to the tumor The stylet is withdrawn and suction is applied using a syringe with lock The needle is pushed into the tumor one or more times The needle is withdrawn with sustained suction A cylinder or larger pieces of tissue should be obtained The biopsy is immediately dropped into a fixative

The reported technique should only be used in patients with advanced tumors where the alternative is biopsy obtained by laparotomy which in

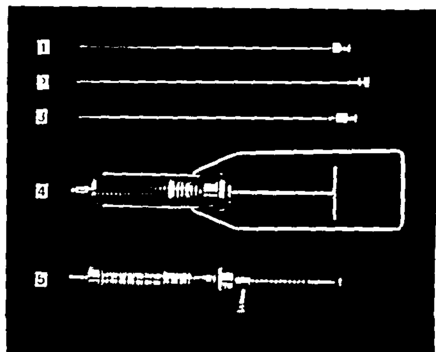


Fig. 1 Instruments for vaginal fine needle and large needle aspiration biopsy (1) Fine caliber needle ( ) Pointed stylet for 3 (3) Large caliber needle (4) 10 cm³ Luer syringe with grip (5) 10 cm³ Record syringe with lock for fixation of piston

these patients is associated with a significant mortality Moreover a laparotomy imposes high risk of disseminating the tumor The risk of spreading tumor cells in the puncture canal is generally considered as negligible in fine caliber needle biopsy but a certain risk of local spread should be considered with increasing caliber although possibly still low However if malignancy is documented nearly all patients will be treated with chemotherapy or regional radiotherapy

To my experience the reported technique is safe and reliable

Jorgen Serup

Department of Obstetrics and Gynaecology
Central Hospital
DK-4800 Nykobing Falster
Denmark

REFERENCES

1 Bagley C M Young R C Canellos G P & DeVita V T Treatment of ovarian carcinoma Possibilities for progress N Engl J Med 287 856 197

2 Brun C *In* Nefro-urologi (ed S E Bergentz F Brodwall & H Lund) p 39 Munksgaard Copenhagen 1973

3 Iversen P & Brun C Aspiration biopsy of the kidney Am J Med *11* 3 4 1951

4 Iversen P & Roholm K On aspiration biopsy of the liver with remarks on its diagnostic significance Acta Med Scand *102* 1 1939

5 Jensen H K Gram N C & Francis D Finnålspunktur som diagnostisk hjælpemiddel ved gynækologiske tumorer Ugeskr Laeger *136* 586 1974

6 Kjellgren O Ångstrom T Bergman F & Wiklund D E Fine needle aspiration biopsy in diagnosis and classification of ovarian carcinoma Cancer 2 9 1971

7 Menghini G One second needle biopsy of the liver Gastroenterology *35* 190 1958

Acta Obstet Gynecol Scand 58 127 1979

ANNOUNCEMENT

INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS

Secretariat 27 Sussex Place London NW1 England

List of National and International Congresses 1979

Date	Place	Name	Office
1979			
January 18 19	San Salvador	First National Congress of Gynaecology and Obstetrics	Final Pasaje 10 Colonia Miramonte San Salvador El Salvador C A
January 28 31	Hot Springs	South Atlantic Association of Obstetrics and Gynecology	American College of Obst & Gyn One East Wacker Drive Chicago Ill 60601 U S A
March 4-9	Bombay	First Asian Congress of Induced Abortion and Voluntary Sterilisation	Dr Jhaveri s Hospital for Women 224 Lady Hardinge Road Matunga Bombay 400 016 India
March 11 17	Hobart	Second Australian & New Zealand Congress of Obstetrics and Gynaecology	J F Correy M D Dept of OB/GYN University of Tasmania Box 252 C Hobart Tasmania 7001 Australia
March 12 13	Paris	*Symposium on uterine cervix cancer*	*Fondation Curie 26 rue d Ulm* 75231 Paris France
March 13 16	Caracas	First Panamerican Congress of Andrology	Secretariat P A N C A C S Mott Center for Human Growth & Development 275 Hancock St Detroit Michigan 48201 U S A
April 4 7	San Francisco	American Fertility Society	American College of Obstetricians & Gyencologists 1 East Wacr Drive Chicago Ill 60601 U S A
May 6-10	Seoul	IVth International Conference on Voluntary Sterilisation	Elizabeth Connell M D The Rockefeller Foundation 1133 Av of the Americas New York N Y 10036 U S A
June [illegible]0	Venice	International Symposium on Fetal Medicine	Prof B Salvadori Dept of OB/GYN University of Parma Parma Italy
June 27 30	Montreux	Congress of the Swiss Society of Gynaecology	Dr H Stamm Geb gyn Abteilung Stadtischen Krankenhaus CH 5400 Baden Switzerland
June 7 30	Amsterdam	International Symposium Medicated IUD s & Polymeric Delivery Systems	Miss K Spanjard Box 0 5340 Oss Holland
October 4 6	Rome	First International Congress on Hormones and Cancer	American Express Company S A I Conversiones Service Italy *Piazza di Spagna 32 00187 Rome Italy*
October 5 31	Tokyo	IXth World Congress of Gynecology & Obstetrics	Congress Secretariat c/o Simul International Inc 1 8 10 Akasaka Minato-ku Tokyo 107 Japan

ANNOUNCEMENT

IXth World Congress of Gynecology and Obstetrics is to be held October 25 31 1979 in Tokyo Japan

Official languages English French Spanish and Japanese

Scientific Program

Special lectures

Reproductive endocrinology by Prof Kenneth J Ryan Harvard Medical School U S A

*Comparative aspects of fetal differentiatio*by Prof Alfred Jost College de France France

Recent progress in gynecologic oncology by Prof Per Kolstad Norwegian Radium Hospital Norway

Plenary sessions

Social aspects of obstetrics and gynecology including contraception

The climacteric and postmenopause including hormone therapy

Endocrinology of the menstrual cycle

Physiopathology of intrauterine fetal growth

Reproductive immunology

The role of obstetric management in reducing fetal mortality and morbidity

Premalignant lesions of the female genital tract

In addition there are *Correlated Seminars Seminars* a*s* *Free Communications* covering wide range of topics of cu rent interest

Social Program and *Program for Accompanying Persons*

Deadlines

Early registration July 31 1979

Application Free communi ation papers films and scientific exhibits February 28 1979

Those who are interested in attending the Congress are in vited to write to

Secretariat
IX World Congress of Gynecology and Obstetrics
c/o Simul International Inc
Kowa Bldg No 9
1 8 10 Akasaka Minato-ku
Tokyo 107 Japan

Acta Obstet Gynecol Scand 58 129–134 1979

DURATION OF LABOUR WITH SPONTANEOUS ONSET

P Bergsjo L Bakketeig and S N Eikhom

From the Department of Obstetrics and Gynaecology Akershus Central Hospital University of Oslo School of Medicine Oslo the Institute of Community Medicine University of Trondheim School of Medicine and the Department of Electronic Data Processing University of Bergen School of Medicine Bergen Norway

Abst act Among 2 242 women with spontaneous onset of labour the median duration of labour for those delivered vaginally was 8 1/4 hours in para 0 5½ hours in para 1 and 4 3/4 hours in para 2+ mothers In the parity groups 0 1 and 2+ 90% had delivered within 16 1/4 hours 10½ hours and 10 3/4 hours respectively while 10% of para 0 labours lasted less than 4 hours 10% of para 1 labours less than 2 1/4 hours and finally 10% of para 2+ labours less than 2 hours In the first stage of labour the latent phase (cervical dilatation less than 4 cm) was nearly 2 5 times as long as the active phase (cervical dilatation 4–10 cm) The second stage (cervical dilatation 10 cm—birth) had a median duration of 16 min in para 0 and approximately 10 min in para 1+ mothers The length of the latent and active phases and the second stage for para 1+ mothers was 60-70% of that of para 0 mothers In individual mothers there were weak correlations between the length of the phases and stages For example the length of the latent phase appeared to be a relatively poor predictor of the length of the active phase of labour However selection bias may have weakened these correlations somewhat

Clinical experience and statistical evidence indicate that the mean duration of labour is considerably shorter than as presented in current Scandinavian textbooks of obstetrics (4 5 8) The duration of labour is influenced by physical factors both maternal and fetal as well as by external interference such as operative delivery and other medical procedures Therefore periodic reassessment of the duration of labour is necessary

Duration of labour is associated with perinatal mortality (6 9) In countries where most deliveries occur in institutions labour of short duration carries the risk of birth occurring during transportation an event which also represents a hazard to mother and child (2) We have recently completed a study of the total duration of labour in women with spontaneous onset based on 1994 cases from Akershus Central Hospital 1974–1975 (1) The median values generally agreed with the averages in other recent reports (6 9 10) being 8 hours 14 min in nulliparae 5 hours 30 min in primiparae and 4 hours 49 min in women with two or more previous births However the variation of the duration of labour appeared to be quite large From a practical point of view the variation of the length of labour is at least as important as is the average duration This is a report on the duration of different stages and phases of labour with spontaneous onset

MATERIAL AND METHODS

2 292 women with spontaneous onset of labour at Akershus Central Hospital during the period September 1 1974 to December 31 1975 were included in the study irrespective of the mode of delivery During the period of study information on each labour was reported on specially designed partograms from which all relevant data were drawn for electronic data processing (3) The course of labour was divided into the first and second stage and the first stage was subdivided into 2 phases namely the latent and the active phase (7) The following definitions were used

Latent phase Time from the onset of labour to first measurement of 4 cm cervical dilatation

The onset of labour was arbitrarily determined as from the occurrence of regular painful uterine contractions less than 10 min apart Cervical dilatations was judged from ordinary vaginal examination

Active phase Time from first measurement of 4 cm cervical dilatation to first measurement of 10 cm (or complete) cervical dilatation

Second stage Time from first measurement of 10 cm (complete) cervical dilatation to complete delivery of the baby

Dilatation of 4 cm was chosen as the dividing point between the latent and active phases as in our study the rate of cervical dilatation was higher after 4 cm than after 3 cm which has previously been used as the dividing point between the two phases Data sufficient to measure the length of one or more of the two phases of the first stage or the length of the second stage of labour were required for inclusion in the analysis and of 2 292 mothers with spontaneous onset of labour 224 met these criteria (964 para 0 875 para 1 and 387 para 2+)

No artificial methods to induce labour were employed

Table I *Fetal presentation at start of labour by parity*
Based on 2242 women with spontaneous onset of labour

Fetal presentation	Para 0		Para 1		Para 2+	
	No	%	No	%	No	%
Occipito-frontal	880	90 5	795	90 5	371	94 6
Occipito-sacral	44	4 5	51	5 8	15	3 8
Median vertex	16	1 6	6	0 7	1	0 3
Brow	–	–	2	0 [illegible]	–	–
Face	–	–	2	0 [illegible]	–	–
Breech	29	3 0	[illegible]0	2 3	5	1 [illegible]
Not stated/unknown	3	0 3	2	0 2	–	–
Total	972	100 0	878	100 0	39[illegible]	100 0

but during the course of labour however artificial rupture of the membranes was a common procedure and oxytocics to enhance labour were occasionally used

As the fetal presentation influences the course and duration of labour the distribution of fetal presentations is given in Table I by parity Approximately 90% of babies of para 0 and para 1 mothers and 95% of the babies para 2+ mothers presented in the occipite anterior position while breech presentation occurred in 3 0% [illegible]3% and 1 3% respectively

The use of operative delivery is an important factor to be considered in the analysis of labour Table II shows the types and frequencies of the various interventions used among the 2242 labours included in the analysis Approximately 20% of para 0 labours and 6–8% of para 1+ labours were terminated by operative intervention Caesarean sections were performed in 1 8% of women with labour of spontaneous onset The majority of these (19 out of [illegible]6) are not included in the analysis However where Caesarean section was performed after the latent phase was completed these labours were included in the analysis and therefore contribute to the estimated length of the latent phase The possible implications of the exclusion of the labours terminated by Caesarean section will be discussed

Fig 1 shows the frequency of intervention during the course of labour for para 0 mothers in whom intervention is far more common than in mothers with one or more previous deliveries The lower curve shows the risk of intervention at each 30 min interval throughout labour The upper curve shows the cumulative frequency of interventions in the course of labour As shown in the figure less than 2% of the labours were terminated by intervention during the first 5 hours of labour implying that the length of the latent phase will be relatively little affected

The length of the active phase however will obviously be affected by intervention since the majority occurred after 7–12 hours duration of labour as shown in Fig 1

RESULTS

The results are shown in Tables III IV and V Since the distribution of the duration of labour within each parity group is somewhat skewed percentile values are used in the tables to describe the distribution instead of mean values and standard deviations

Table II *Mode of delivery by parity*
Based on [illegible]242 women with spontaneous onset of labour

Mode of delivery	Para 0		Para 1		Para [illegible]	
	No	%	No	%	No	%
Spontaneous	780	80 2	810	9[illegible] 3	368	91 9
Forceps (cephalic presentation)	1[illegible]	1 2	1	0 1	–	–
Vacuum extraction	114	11 7	19	2 2	[illegible]	1 3
Caesarean section	4	0 4	[illegible]	0 2	1	0 3
Breech extraction partial	[illegible]1	[illegible]	18	[illegible] 1	5	1 3
Breech extraction total	6	0 6	–	–	–	–
Other interventions	9	0 9	8	0 9	5	1 3
More than one intervention	5	0 5	[illegible]	0 [illegible]	–	–
Not stated/unknown	21	2 2	18	[illegible] 1	8	[illegible] 0
Total	972	100 0	878	100 0	39	100 0

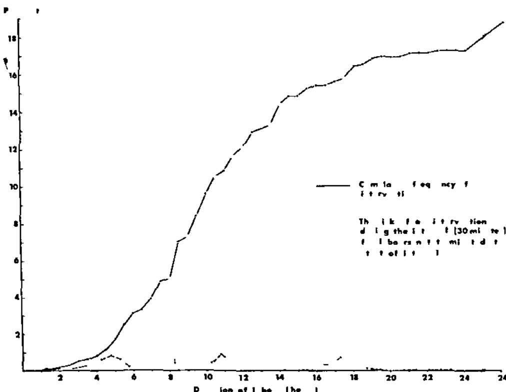


Fig 1 The risk and cumulative frequency of interventions during labour for 877 para 0 women with known total duration of labour

The median total duration of labour was 8 hours 14 min 5 hours 30 min and 4 hours 40 min in para 0 para 1 and para 2+ mothers respectively based on all mothers with known total duration of labour

For 10% para 0 mothers labour lasted less than 3 hours 51 min and for 10% of mothers more than 16 hours As shown in Table III the median duration of the latent phase for para 0 mothers was 5 hours and 45 min the median duration of the active phase was slightly less than 2½ hours and the median length of the second stage was 16 min The corresponding durations are shown in Table IV for para 1 mothers and in Table V for para 2+ mothers The median durations of the latent and active phases and the second stage relative to that of para 0 mothers are approximately 70% for para 1 mothers and 60% for para 2+ mothers as shown in Table VI However the relative differences between the parity groups are slightly less for the duration of the latent phase compared to the active phase and the second stage

Table III *Duration of labour with spontaneous onset in para 0 women related to stage and phase*

	First stage							
	Latent phase (n=466)		Active phase (n=497)		Second stage (n=946)		Total duration (n=877)	
Per centile	h	min	h	min	h	min	h	min
10th	[illegible]	00	0	55	0	00	3	51
50th	5	45		6	0	16	8	14
90th	1[illegible]	2[illegible]	4	58	0	44	16	10

The median duration of the latent phase (as defined in this study) is approximately 2.5 times the length of the active phase and dose not differ significantly between the three parity groups. However the length of the latent phase seems to be slightly less affected by parity compared to the active phase and the second stage of labour. The relatively weak correlation between the duration of the stages and phases of labour within individual mothers may be considered an unexpected finding. It would not have been surprising to find a relatively strong correlation between for example the duration of the latent and active phases. We have considered whether possible biases in our data selection could lead to a weakening of such correlations. Here we have to keep in mind that the correlation between the length of the latent and the active phases as shown in this study is based on less than 40 per cent of all the labours with spontaneous onset, namely the group of mothers with known durations of the two phases. Among the mothers not included in this group there exist at least two categories of labours which if included may contribute to an increased correlation of the lengths of the two phases. One of these consists of labours with extremely long latent phase which are terminated during the active phase by some intervention. The other category consists of those with very short duration of both phases and thereby reduced chances of a vaginal examination being performed at the time when cervical dilatation had reached exactly 4 cm. However to what extent exclusion of these groups of labours has decreased the correlation is hard to estimate. It is difficult to imagine any bias in the selection of labours that could have led to an increased correlation. Our conclusion therefore is that there is a weak but significant correlation between the duration of the latent and the active phases and also between the duration of the active phase and the second stage of labour. For clinical purposes the duration of one stage is of little help in predicting the duration of the next.

ACKNOWLEDGMENT

This investigation has been supported be a grant from the Norwegian Research Council for Science and the Humanities. The study had been carried out in collaboration with professor Tor Bjerkedal and the Medical Birth Registry of Norway, Institute of Hygiene and Social Medicine, University of Bergen and data processing was obtained through Department of Electronic Data Processing, University of Bergen, School of Medicine.

REFERENCES

1 Bakketeig L S, Eikhom S N & Bergsjø P. Duration of labour starting spontaneously. (In Norwegian.) Tidsskr Nor Laegeforen 97: 44?, 1977.
2 Bakketeig L S & Bjerkedal T. Birth during transportation. (In Norwegian.) Tidsskr Nor Laegeforen 94: 2306, 1974.
3 Bergsjø P, Bakketeig L S & Bjerkedal T. Birth registration by partogram. (In Norwegian.) Tidsskr Nor Laegeforen 95: 439, 1977.
4 Bjøro K & Molne K. Propedeutisk obstetrikk. Universitetsforlaget, Oslo, 197?.
5 Brody S. Obstetrik og gynekologi. Almqvist & Wiksell, Stockholm, 1970.
6 Daring G K & Krauss V. Über die Bedeutung der Geburtsdauer für das Kind. Geburtshiefe Frauenheilk 27: 1185, 1967.
7 Friedman E A. Labour Clinical Evaluation and Management. Appelton-Century-Crofts, Division of Meredith Publishing Company, New York, 1967.
8 Larsen J F, Asbjørn P & Schmidt T. Obstetrik/gynaekologi. Munksgaard, København, 1974.
9 Niswander K R & Gordon M (eds.) The Women and Their Pregnancies. U.S. Department of Health, Education and Welfare Publication No. (NIH) 73-379, Washington D.C., 1972.
10 Studd J. Partograms and Nomograms of Cervical Dilatation in Management of Primigravid Labour. Br Med J 4: 451, 1973.

Submitted for publication Feb. 20, 1979

Per Bergsjø, M.D.
Department of Obstetrics and Gynecology
Akershus Central Hospital
1474 Nordbyhagen
Norway

Acta Obstet Gynecol Scand 58 135–139 1979

ꞓNTAL EPIDURAL ANALGESIA IN LABOUR RELATED HE PROGRESS OF LABOUR FETAL MALPOSITION AND INSTRUMENTAL DELIVERY

R Jouppila P Jouppila J M Karinen
and A Hollmen

*ı the Departments of Anaesthesiology and Obstetrics and Gynaecology
University of Oulu Oulu Finland*

Abstract The w-dose continuous segmental epidural analge ıng the first stage of labour on the progress of frequency of fetal malpositions and the rate of ractions was studied prospec tively in 100 par dural group) The results were compared with 1 s given none or conventional analgesia (contro e results showed that in the primiparous epidu e progress of labour before analgesia was induc ificantly slower than in the control group After however the subsequent course of the labour duration in both groups The durations of the of labour did not differ significantly between The differences in fetal malpositions at deliv tistically insignificant Nor did the rate of ractions 8% in the primiparous and 0% n ous epidural group differ statistically from t ding rate in the con trol groups The result rmal progress and outcome of labour after lo ntal epidural anal gesia

Segmental epidural analg the height of T 10–12 relieves pain ve during the first stage of labour Dur d stage the mothers may experience is type of analgesia but they have a go wn reflex and can actively take part in Most of the mothers consider the fir bour the most painful and want effectiv recisely during this stage (6) This fa ommon obstetric practice in Scandin avoids unnecessary instrumental de the reason why segmental epidural ad of caudal or lumbar analgesia has the routine obstetric epidural techn Oulu University Hospital since 1972 pen ence has been good (7) In calbar epidural analgesic techniques the and caudal segments are also blocke of analgesic agents are generally the bearing-down reflex is poor or absent during the second stage resulting in an increased incidence of instrumental deliveries (2 8 16) It has also been claimed that in addition to an increased number of instrumental deliveries caudal and lumbar epidural analgesias might prolong the progress of labour The frequency of fetal malpositions in connection with lumbar epidural analgesia has also been shown to be increased (8 16)

The aim of the present prospective study was to find out the effect of segmental epidural analgesia accomplished with low doses of bupivacaine on the duration of the different stages of labour the fre quency of fetal malpositions at delivery and the rate of vacuum extractions

MATERIAL AND METHODS

The series consists of 100 parturients given segmental epidural analgesia (epidural group) and 100 parturients given none or conventional analgesia (control group) These cases were selected in such a way that the first 100 parturients given segmental epidural analgesia in 1977 in the Oulu University Central Hospital were taken as the objects of this prospective study The control group was selected so as to give each epidural parturient a matched control as regards parity and the fact of whether the labour was induced or spontaneous 77 of the parturients in each group were primiparous and 23 multiparous The mean age parity and number of gestational weeks as well as the pregnancy complications of the parturients are shown in Table I

39 of the primiparous labours in both groups were in duced with i v oxytocin infusion and/or with amniotomy In 37 spontaneous primiparous labours in the epidural group oxytocin was used for augmentation of the labour The corresponding number in the primiparous control group was 24 (Table II) Of the multiparous labours 17 were induced in both groups Of the spontaneous multiparous labours with epidural analgesia oxytocin was used in five cases whereas in the control group none of

ˀı on segmental epidural analgesia

ς	Primi parae (N=77)	Multi parae (N=ˀˀ)
esia	Th₁ ₂	Th ₀₋₁
l puncture	L_1–L_2	L_1–L_2
ion at the		
nalgesia		
	3 7	3 5
	2–7	ˀ–6
5ˀ		
ed (ml)		
	5 8	4 9
	4–12	4–16
on	At least 15 lateral tilt	left
fall nitial pressure)	6 cases (8ˀ)	3 cases (13%)

Abstract The
epidural analge
the progress of
and the rate of
tively in 100 par imiparous parturients in the different
compared with I differ statistically significantly from
analgesia (contro
primiparous epidu cond stage of more than 30 min in
analgesia was induc n in 7 (9%) of the primiparous
control group Afte and in 5 (7%) of the primiparous
course of the labour
The durations of the
significantly between arturients the duration of the dif
malpositions at deliv
Nor did the rate of
primiparous and 0% u
differ statistically from t
trol groups The result
outcome of labour after lo
gesia

(± S D) durations of the different st

Primiparae		
pidural oup =77)		Control group (N=77)
±310	P<0 01	469±205
ˀ1ˀ	ns	15±10
116	ns	ˀˀ2±1ˀ5
15	ns	11±4

Segmental epidural analg
In 10–12 relieves pain ve
first stage of labour Dur
mothers may experience
analgesia but they have a go
and can actively take part in
the mothers consider the fir
most painful and want effectiv
during this stage (6) This fa
obstetric practice in Scandin
unnecessary instrumental de
reason why segmental epidural
caudal or lumbar analgesia has
routine obstetric epidural tech
University Hospital since 1972 ˀ
ence has been good (7) In c
epidural analgesic techniques the
caudal segments are also blocke
analgesic agents are generally

al malposition at delivery a

Primiparae	
Epidural group (N=77)	
6 (8%)	ns
3	
2	
1	
6 (8ˀ)	ns

Table VI *Apgar scores and birthweights (g) of the newborns*

	Primiparae			Multiparae		
	Epidural group (N=77)		Control group (N=77)	Epidural group (N=23)		Control group (N= 3)
Apgar scores (*mean* ± S D)						
5 min	8 7±0 7	ns	8 9±0 7	9 ?±0 5	ns	9 1±0 9
15 min	9 3±0 6	ns	9 2±0 5	9 2±0 4	ns	9 4±0 5
Number of babies with Apgar scores ≤7						
5 min	5	ns	3	0	ns	1
15 min	0	ns	1	0		0
Birthweight (mean ± S D)	3 5?1±461		3 544±446	3 707±521	ns	3 677±53

statistically significant differences between the groups in the Apgar scores taken at the stated times nor in the birthweights of the babies

DISCUSSION

Lumbar epidural analgesia with high doses of the analgesic agent has been shown to prolong the duration of labour especially if it has been begun too early but *segmental* epidural analgesia has no such effect on the progress of labour (2 3 9) Our find verify this The present results show that *ental* epidural analgesia with small doses of ivacaine has no prolonging effect on the duration of labour after the block It can be seen that although the primiparous parturients having epidural analgesia had a longer total first stage when compared with their controls the I–D intervals were similarly short Thus probably due to the pains in the primiparous epidural group the progress of labour before the analgesia was significantly slower than in the controls After the block however because of the disappearance of pain apprehension etc the subsequent course of labour was similar in the two groups This shows that pain relief with an effective analgesic method such as *segmental* epidural analgesia normalizes the progress of the long first stage in painful labours which otherwise could be even more prolonged In the present study pain relief was the main distinguishing feature of the groups for in our hospital pain is the main indication for segmental epidural analgesia Our findings agree with those of Phillips et al (15) who showed the labour curves in connection with epidural analgesia were normal

One of our aims in using *segmental* epidural analgesia at the height of Th 10–12 during the first stage of labour is to retain the second stage as normal The mother has a normal bearing-down reflex a she can actively take part in the delivery Our su cess in this respect is shown by the present finding there were no differences in the duration of th second stage of labour between the epidural a control groups However in a series where th *lumbar* epidural technique is used the second sta is prolonged (3 9) Crawford (3) in his large seri noted that 50% of the primiparous epidural part nents had a second stage longer than 50–60 mi while in our series the active second stage on exceeded 30 min in 9% of the primiparous epidur parturients which is a clear advantage of our tec nique

The frequency of fetal malpositions in the prese group of epidural patients was low and did not diffe from the corresponding control parturients Maltau & Andersen (11) similarly found no evidence of a high incidence of fetal malpositions in connection with selective epidural block However in series where the *lumbar* epidural technique has been used with higher doses of the analgesic agent the frequency of fetal malpositions have been higher tha ours (8 16) The reason for the increased number of malpositions of the fetal head after a more extensive epidural block could be disturbance of rotation and flexion of the fetal head associated with relaxation of the pelvic floor (2) Our results are a natural consequence of our *segmental* epidural technique where the integrity of the pelvic floor is preserved

The incidence of vacuum extractions in our epidural groups was very low (8% in the primiparous epidural parturients) and there were no statistical differences between that and the incidence in the control groups In the series of Doughty (4) and Maltau & Andersen (11) where a

selective epidural technique was used the rate of instrumental deliveries was 20% and in other series it has been even higher (8 16) Thus our present incidence and that reported by Hollmen et al of 7 4% (7) from our hospital are lower than in any similar series previously published and are clearly due to our segmental technique

Maternal hypotension (a fall in the systolic blood pressure ≥25% from the initial) occurred in 8% and 13% of the epidural parturients these are lower frequencies than those reported by other authors (15) and also lower than in a previous series examined in our hospital (7) In our opinion this relatively low frequency is mainly due to the strict avoidance of the maternal supine position after the block The blood loss at delivery did not show any differences between the epidural and the control groups This finding corresponds to the observation of Maltau & Andersen (11) The clinical condition of the newborn infants in our series was good and also showed no differences between the epidural and the control groups This finding also agrees with the earlier reports that the neonates of mothers who had been given epidural analgesia were in an equally good or even better clinical condition than the babies of control mothers (1 5 10 12 14 17 18)

In conclusion we can state that segmental epidural analgesia at the height of Th 10–12 given for pain relief during the first stage of labour does not seem to disturb the normal progress of labour Nor can it be shown to increase the frequency of fetal malpositions nor instrumental deliveries

REFERENCES

1 Belfrage P Raabe N Thalme B & Berlin A Lumbar epidural analgesia with bupivacaine in labour Am J Obstet Gynecol *121* 760 1975
2 Bonica J J Spinal (Lumbar) epidural block *In* Principles and Practice of Obstetric Analgesia and Anesthesia p 612 E A Davis Co Philadelphia 1972
3 Crawford J S The second thousand epidural blocks in an obstetric hospital practice Br J Anaesth *44* 1277 1972
4 Doughty A Selective epidural analgesia and forceps rate Br J Anaesth *41* 1058 1969
5 Hollmen A Lumbar epidural analgesia as an obstetric analgesic method Acta Anaesthesiol Scand Suppl *37* 251 1970
6 Hollmén A Hollmén U Pihlajaniemi R Sjöstedt E & Vaherva T Labor pain experienced by the mothers and eventual possibilities to alleviate it Suomen Lääkarilehti—Finlands lakartidning *25* 3126 1970
7 Hollmén A Jouppila R Pihlajaniemi R Karvonen P & Sjostedt E Selective lumbar epidural block in labour A clinical analysis Acta Anaesthesiol Scand *21* 174 1977
8 Hoult I J MacLennan A H & Carrie L E S Lumbar epidural analgesia in labour relation to fetal malposition and instrumental delivery Br Med J *1* 14 1977
9 Johnson W L Winter W E Eng M Bonica J J & Hunter C A Effect of pudendal spinal and peridural block anesthesia on the second stage of labor Am J Obstet Gynecol *113* 166 1972
10 Jouppila R & Hollmén A The effect of segmental epidural analgesia on maternal and foetal acid–base balance lactate serum potassium and creatine phosphokinase during labour Acta Anaesthesiol Scand *20* 259 1976
11 Maltau J M & Andersen H T Continuous epidural anaesthesia with a low frequency of instrumental deliveries Acta Obstet Gynecol Scand *54* 401 1975
12 McDonald J S Bjorkman L L & Reed E L Epidural analgesia for obstetrics Am J Obstet Gynecol *120* 1055 1974
13 Moore D C Bridenbaugh L D Bridenbaugh P O & Tucker G T Caudal and epidural blocks with bupivacaine for childbirth Report of 657 parturients Obstet Gynecol *37* 667 1971
14 Noble A D Craft I L Bootes J A H Edwards P A Thomas D J & Mills K L M Continuous lumbar epidural analgesia using bupivacaine a study of the fetus and newborn child Br J Obstet Gynecol *78* 559 1971
15 Phillips J C Hochberg C J Petrakis J K & Van Winkle J D Epidural analgesia and its effects on the "normal" progress of labor Am J Obstet Gynecol *129* 316 1977
16 Raabe N & Belfrage P lumbar epidural analgesia in labour A clinical analysis Acta Obstet Gynecol Scand *55* 125 1976
17 Thalme B Belfrage P & Raabe N Lumbar epidural analgesia in labour I Acid–base balance and clinical condition of mother fetus and newborn child Acta Obstet Gynecol Scand *53* 27 1974
18 Zador G & Nilsson B A Low dose intermittent epidural anaesthesia with lidocaine for vaginal delivery II Influence on labour and foetal acid–base status Acta Obstet Gynecol Scand Suppl *34* 17 1974

Submitted for publication April 24 1978

Riitta Jouppila M D
Dept of Anaesthesiology
University of Oulu
90220 Oulu 22
Finland

Acta Obstet Gynecol Scand 58 141–146 1979

PREGNANCY FOLLOWING TREATMENT WITH HUMAN GONADOTROPINS IN PRIMARY UNEXPLAINED INFERTILITY

Chun Fu Wang and Carl Gemzell

From the Department of Obstetrics and Gynecology Downstate Medical Center State University of New York Brooklyn New York USA

Abstract Six patients with primary unexplained infertility of 2 to 9 years duration and who failed to conceive after repeated trials of clomiphene treatment were treated with human gonadotropins 3 of them became pregnant following one or two courses of treatment Three patients failed to conceive in spite of 3 courses of human gonadotropins 2 of them had high titers of sperm agglutinating antibodies found in their sera which may explain their infertility None of the 13 treatments resulted in hyperstimulation syndrome or multiple births This preliminary result seems encouraging but awaits further study

Even after a thorough infertility work up no definite cause could be found in some infertile couples While some of these couples may achieve a pregnancy without therapy the majority of them continue to be childless year after year Clomiphene has been used empirically to achieve pregnancy in some of these couples (1 2) In this report six patients with primary unexplained infertility and who failed to conceive after repeated trials of clomiphene treatment were treated with human gonadotropins three of them became pregnant following one or two courses of treatment

MATERIALS AND METHODS

Six infertile patients who were referred for further investigation and treatment during 1976 and 1977 were included in this report All of the patients have been properly and thoroughly evaluated including semen analysis of husband recorded basal body temperature timed endometrial biopsies postcoital tests hysterosalpingograms appropriate hormonal assays and laparoscopy by the referring physicians They have failed to conceive with empirical clomiphene treatment and have been told that human gonadotropins therapy may be helpful

A detailed history was obtained and a thorough physical examination was performed on every couple Semen analysis was repeated and demonstration of sperm agglutinating antibodies by a simple and sensitive microagglutination technic (MAT) according to the method of Friberg (3) were studied in serum from men and women in seminal fluid and in certain cervical mucus Postcoital tests were performed during the treatment

hMG (Pergonal Serono Laboratories Inc Boston Mass) was administered intramuscularly daily beginning on the 4th or the 5th day of the cycle The initial dosage was 2 ampules per day (Pergonal contains 75 IU of FSH and 75 IU of LH per ampule) The dosage as well as the duration of hMG administration was determined by frequent pelvic examination and daily (Monday through Friday) determination of plasma estradiol 17β (E_2) When plasma E_2 concentration had risen to 350 pg per milliliter or more and after a continuous rise of four to five days further hMG was withheld and ovulation was effected by the administration of 10 000 IU of hCG (Pregnyl Organon Inc NJ) Ovulation was confirmed by an elevation of the basal body temperature and the determination of plasma progesterone concentration according to Johansson (4) A second injection of 5 000 IU hCG was given one week later The patient was instructed to have intercourse the day before the day during and the day after the first hCG injection Single intrauterine pregnancy was confirmed by radioreceptor assay for hCG and pelvic sonogram

Daily plasma sample for E was obtained between 9 00 and 9 30 a m by venipuncture The plasma samples were assayed on the same day they were obtained according to the radioimmunoassay method of Enqvist & Johansson (5)

CASE REPORT

Case 1 (M K)

M K a 29-year-old white female para 0000 was seen with the chief complaint of primary infertility of 3 years duration

The patient had menarche at 12 and periods were always regular with 30 days interval Her period lasted for 5 days and no dysmenorrhea was noted In 1973 following her marriage she took oral contraceptives for 9 months then discontinued without apparent problem The infertility work up and pelvic examination were essentially normal

Both patient and her husband were treated with Vibramycin Then she was treated with clomiphene ranged from 100 mg to 150 mg daily for 5 days in each treatment cycle with or without hCG for 5 months She ovulated

regularly with good postcoital test and normal luteal phase but failed to conceive

She was given hMG–hCG treatment and she conceived following the first course of treatment

Case 2 (S F)

S F a 3? year-old white female para 0000 was seen with the chief complaint of primary infertility of 5 years duration

The patient had menarche at 12 and periods were regular with intervals ranging from 28 to 32 days In 1970 following her marriage she took oral contraceptives for 3 years then discontinued without apparent problem Past medical history revealed that she had acne and has been treated with tetracycline and ultraviolet for several years

The infertility work up and pelvic examination were normal Laparoscopy was done in September 1974 and laparotomy was followed for lysis of peritubal adhesion and excision of right ovarian fibroma

Following laparotomy she was treated with clomiphene ranged from 50 mg to 150 mg daily for 5 days with or without hCG in each treatment cycle intermittently for nearly 3 years Repeated hysterosalpingogram in April 1977 revealed normal uterus and bilateral patent tubes No sperm agglutinating antibodies were found

She was given hMG–hCG treatment and conceived following the first course of treatment without complication

Case 3 (C H)

C H a 29-year-old white female para 0000 was seen with the chief complaint of primary infertility of two years

The patient had menarche at 13 and periods were regular with intervals of 3? to 33 days Mild dysmenorrhea was noted In 1975 following her marriage she took oral contraceptives for one year then discontinued without any problem

Semen analysis in March 1977 revealed 1 ml in volume with 53 1 million/ml and 70% motility Morphological study of sperm on stained smear revealed 42% normal forms 18% tapering forms and 32% amorphous forms Repeated semen analysis in May 1977 revealed 1 ml in volume with 89 million/ml and 50% motility Morphological study of sperm on stained smear again showed 38% normal forms 45% tapering forms 9% amorphous forms and 8% immature forms In spite of some question found in sperm morphology the postcoital tests were satisfactory on 2 occasions

She had normal hysterogram in March 1977 Endometrial biopsy and luteal phase plasma progesterone levels revealed no evidence of luteal phase defect Laparoscopy was done in April 1977 and was found to be essentially normal pelvis No sperm agglutinating antibodies were found

She was treated with clomiphene 100 mg daily for 5 days in 2 consecutive cycles She ovulated normally and luteal phase was normal in duration but failed to conceive She was given hMG–hCG treatment in May 1977 She had temperature elevation for ?0 days and period came down after severe cramp Unfortunately a specific and sensitive hCG assay was not performed to detect an eventual pregnancy In August 1977 she was treated again with hMG–hCG and conceived

Case 4 (B W)

B W a 28 year-old white female para 0000 was seen with the chief complaint of primary infertility of 5 years duration

The patient had menarche at 13 and periods were regular ranging from 26 to 27 days with no dysmenorrhea In 1967 following her marriage she took sequential oral contraceptives for about 2 years then discontinued without apparent problem Following oral contraceptives she used diaphragm for contraception for another 3 years

The infertility work up and pelvic examination were normal Culdoscopic examination revealed essentially normal pelvis Cervical culture for T Mycoplasma was negative Semen analysis was normal but 1 8 sperm agglutinating antibodies was found in the patient s serum She was treated with clomiphene 100 mg daily for 5 days in 2 consecutive cycles but failed to conceive

Repeated semen analysis was normal and no sperm agglutinating antibodies was found in February 1975 She was elected to observe for 6 months

She was given hMG–hCG treatment in August and October 1975 She ovulated both times and the treatment went smoothly without any complication The postcoital tests during the treatment were normal but she did not conceive The total dose of hMG each time was [illegible] ampules and was administered for 7 days

Repeated sperm agglutinating antibodies tests in February 1976 revealed negative in her husband's serum seminal fluid and cervical mucus but positive in the patient s serum with a titer of 1 512 (head to head agglutination) She was treated with Vibramycin and clomiphene ranged from 100 mg to [illegible]00 mg daily for 5 days with hCG for 3 cycles The postcoital tests on several occasions were within normal limits She was treated again with hMG–hCG in August 1976 but she failed to conceive

Case 5 (D W)

D W a 29-year-old white female para 0000 was seen with the chief complaint of primary infertility of 5 years duration

She had menarche at 10 and periods were regular with interval of 29 days Mild dysmenorrhea was noted

The infertility work up and pelvic examination were normal No sperm agglutinating antibodies was demonstrated Laparoscopic examination was done in March 1976 and essentially normal pelvis was found She was treated with clomiphene 100 mg daily for 5 days in each treatment cycle for 6 months She ovulated normally with normal luteal phase but failed to conceive

Repeated semen analysis in October was normal and no sperm agglutinating antibodies was found The patient and her husband were treated with Vibramycin Then she was given clomiphene [illegible]00 mg daily for 5 days followed by hCG injection for 3 consecutive cycles The postcoital tests on several occasions during the treatments were satisfactory but she did not conceive

She was given hMG–hCG treatment three times between October 1976 and February 1977 She ovulated each time in the expected time and the treatment went smoothly without any complication but she failed to conceive She had [illegible]0 days luteal phase following the first hMG–hCG treatment It might be an early miscarriage

Table 1 *Clinical features*

Name	Age	Parity	Married (y)	Infertile (y)	History of contraception	Menstrual period
M K	29	0000	4	3	O C (9 months)	Regular q 30 days
S F	32	0000	8	5	O C (2 years)	Regular q 28–32 days
C H	24	0000	2½	2	O C (6 months)	Regular q 30–34 days
B W	28	0000	10	5	O C (2 years)	Regular q 26–27 days
D W	29	0000	5	5	O C (2 years)	Regular q 29 days
Y P	33	0000	9	9	–	Regular q 25–28 days

abortion Unfortunately a specific and sensitive hCG assay for detection of an eventual pregnancy was not performed

Case 6 (Y P)

Y P a 33 year-old white female para 0000 was seen with the chief complaint of primary infertility of 9 years duration

She had menarche at 12 and periods were regular ranging from 26 to 28 days No significant medical or surgical *problem was noted*

The infertility work up was normal except the postcoital tests were poor on some occasions She underwent laparoscopic examination with chromotubation in 1972 and pelvis was found to be normal

She was treated with clomiphene ranged from 50 to 200 mg daily for 5 days with or without hCG from March 1973 to June 1976 intermittently During this period artificial insemination with husband's semen (AIH) was tried for 4 cycles Low dose estrogen treatment during follicular phase was also given in some treatment cycles In spite of extensive therapeutic manipulation she failed to conceive

She was given hMG–hCG treatment for 3 cycles in early 1977 She ovulated each time and the treatment went smoothly without any complication In spite of satisfactory postcoital tests during the treatment she failed to conceive

Repeated semen analysis was normal in June 1977 *However* sperm agglutinating antibodies with titer of 1 512 (head to-tail agglutination) was found in the patient s serum No sperm-agglutinating antibodies was demonstrated in her husband s serum or in seminal fluid

RESULTS

Table I summarizes the pertinent clinical information in each patient The age of the women varied between 24 and 33 years and the duration of infertility between 2 and 9 years None of the 6 patients *had* been pregnant and 5 out of 6 patients have been using oral contraceptives for a period of 6 months to 2 years before they attempted to conceive All 6 patients have regular ovulatory cycles with no evi*dence of luteal phase defect as indicated by re*corded basal body temperature timed endometrial biopsies and plasma progesterone levels

The results of infertility investigation are shown in Table II All 6 patients had normal semen *analysis luteal phase hysterosalpingogram and* adequate postcoital tests Four patients (C H B W D W and Y P) had essentially normal pelvis on laparoscopy while patient S F had lysis of peritubal adhesion by laparotomy 3 years prior to the treatment Clomiphene ranged from 50 to 200 mg daily for 5 days in each cycle with or without hCG having been used empirically to improve the chance of conception by the referring physician in all 6 patients and two of them have been treated with Vibramycin

Table III summarizes the amount and duration of hMG administration as well as the result of treatment The total amount of hMG varied between 11 to 43 ampules and the duration of administration between 7 and 14 days All the treatments resulted in ovulation at the expected time Patient M K and S F conceived following the first course of hMG–hCG treatment and patient C H conceived following the second course of treatment All 3 patients had single intrauterine pregnancy Two of the treatments resulted in 20 days luteal phase it might be an early spontaneous abortion Three patients failed to conceive in spite of 3 courses of hMG–hCG treatment but 2 of them (B W and Y P) had high titers of sperm agglutinating antibodies found in their sera which may explain their infertility None

Table II *Results of infertility investigation and previous treatment*

Name	Semen analysis	Sperm agglutinating antibodies	Luteal phase	Post coital test	Hystero-salpingo-gram	Laparoscopy	Previous treatment
M K	Normal	Negative	Normal	5+	Normal	Not done	Clomid 4× Vibramycin
S F	Normal	Negative	Normal	5+	Normal	Lysis of peri tubal adhesion in 1974 by laparotomy	Clomid on & off ×3 y
C H	Normal	Negative	Normal	4+	Normal	Normal	Clomid 5×
B W	Normal	In wife's serum 1 51?	Normal	3+–5+	Normal	Normal (culdoscopy)	Clomid & hCG 4
D W	Normal	Negative	Normal	3+	Normal	Normal	Clomid & hCG 9 Vibramycin
Y P	Normal	In wife's serum 1 51?	Normal	3+	Normal	Normal	Clomid & hCG 6×

0+ No sperm found 1+ single sperm non motile 2+ single sperm motile 3+ 1–5 motile sperms per hpf 4+ 6–9 motile sperms per hpf 5+ >10 motile sperms per hpf

of the 13 treatments resulted in hyperstimulation syndrome or multiple births

DISCUSSION

Unexplained or idiopathic infertility is used to describe the situation that exists when complete evaluation of the infertile couple reveals no discernible etiologic factors The previously reported incidence was between 10 and 17 6% (1 6–8) Recently laparoscopy has been used as an essential final step in an otherwise negative work up for infertility In spite of this approach the incidence of unexplained infertility is still around 5 to 10% (9–10) Failure to delineate the cause is not surprising as many questions pertaining to reproductive failure are presently unanswerable and untestable The management of this group of infertile patients is indeed very frustrating and the prognosis is poor Jones (11) has found that patients who have had three year pregnancy exposure with no factor to explain the infertility have a pregnancy rate of less than 10% in contrast to those with treatable factors who have a pregnancy rate of about 45%

Based on the experience with a number of referred patients it seems not an uncommon practice to treat patients with unexplained infertility and normal ovulatory cycle with clomiphene in an effort to correct their infertility However the results of the treatment have seldomly been reported Dye

Table III *Results of treatment*

Name	No of treatment	Dosage of hMG (ampules)	Duration of treatment (days)	Result
M K	1	22	11	Single intrauterine
S F	1	18	9	Single intrauterine
C H	2	4	12	Luteal phase 20 days
		18	9	Single intrauterine
B W	3	14	7	Not pregnant
		14	7	Not pregnant
		11	7	Not pregnant
D W	3	21	9	Luteal phase 20 days
		43	14	Not pregnant
		0	7	Not pregnant
Y P	3	18	9	Not pregnant
		29	11	Not pregnant
		24	9	Not pregnant

hMG (Pergonal) contains 75 IU of FSH and 75 IU of LH per ampule

al (1) reported 11 out of 117 patients (9 4%) with no obvious cause of infertility conceived after one empirical course of clomiphene Garcia et al (2) concluded that there is no place for clomiphene therapy for infertility when there is no evidence of ovarian dysfunction

The reasons for patients with normal ovulatory cycle conceived following hMG hCG or clomiphene treatment are unclear Dodson et al (12) studied the plasma sex steroids and gonadotropin profiles in 6 infertile patients with apparent ovulatory cycles and found that they produced insufficient corpora lutea which appeared to be predetermined by ovulation of poorly grown follicles Treatment with clomiphene appeared to produce increased follicular growth and more active corpora lutea It is possible that subtle ovarian dysfunction is present in these infertile patients and cannot be detected by present available clinical tests

It is our speculation that hMG-hCG treatment can improve the chance of conception in patients with unexplained infertility by 1) promoting ovarian follicular growth to achieve good ovulatory response 2) producing an active corpus luteum and a normal luteal phase 3) improving the quality and quantity of cervical mucus to achieve the optimal condition for sperm migration and penetration In this aspect hMG-hCG treatment is superior to clomiphene treatment since the anti-estrogenic effect of clomiphene may impair the cervical mucus and 4) providing the accurate timing of intercourse

Patients M K and S F conceived following the first course while patient C H conceived following the second course of hMG-hCG treatment Patient C H had luteal phase of 20 days with severe menstrual cramp following the first treatment this may represent an early spontaneous abortion It seems that if the patient is going to conceive with the treatment it usually takes place in the first or second treatment Three patients failed to conceive in spite of hMG-hCG treatment and 2 of them have significant titer of sperm agglutinating antibodies in their sera The relevance of sperm agglutinating antibodies to infertility in women is uncertain (13) However in a subgroup of 88 women with unexplained infertility lasting 3 or more years Jones (14) found that those whose serum contained sperm agglutinating antibodies had significantly lower pregnancy rate (37 7% vs 18 5%) as compared to those whose serum was without sperm agglutinating antibodies Therefore the presence of sperm agglutinating antibodies in these patients may explain their failure of treatment The failure of treatment in patient D W is still unknown The preliminary result seems encouraging but awaits further study

None of the 13 treatments with human gonadotropins in this report resulted in hyperstimulation syndrome or multiple births From this and our previous experiences (15) it seems that the normal ovulatory ovary in contrast to the polycystic ovary has an inborn mechanism which controls the number of follicles usually one that goes to full maturation and rupture The polycystic ovary is more sensitive to human gonadotropins and the hyperstimulation syndrome and/or multiple births are more common

It is interesting to note that 5 out of 6 patients with primary unexplained infertility have been on oral contraceptives for a period of time before they attempted to conceive None of the patients has postpill amenorrhea A temporary impairment of fertility after the use of combined oral contraceptives has been reported by the Royal College of General Practitioners in England (16) A year after taking the last pill 20% of nulliparous and 10% of parous women had failed to conceive If one allows for an incidence of 10% of natural infertility among nulliparous women this indicates that one in 10 women experiences impairment of fertility for at least a year after using combined oral contraceptives The reason for this temporary impairment of fertility after oral contraceptives is not clear Nevertheless further study is necessary to clarify the significance of this association

REFERENCES

1 Dor J Homburg R & Rabau E An evaluation of etiologic factors and therapy in 665 infertile couples Fertil Steril 28 718 1977
2 Garcia J Jones G S & Wentz A C The use of clomiphene citrate Fertil Steril 28 707 1977
3 Friberg J A simple and sensitive micro-method for demonstration of sperm agglutinating activity in serum from infertile men and women Acta Obstet Gynecol Scand Suppl 36 21 1974
4 Johansson E D B A simplified procedure for the assay of progesterone Acta Endocrinol (Kbh) Suppl 147 188 1970
5 Enqvist I E & Johansson E D B Radioimmunoassay of oestrone and oestradiol in human and bovine plasma Acta Endocrinol (Kbh) 71 716 1972
6 Jones G S & Pourman K An evaluation of etiologic factors and therapy in 555 private patients with primary infertility Fertil Steril 13 398 1962

7 Case A L & Zuspan F P Infertility Surg Clin North Am 49 121 1969
8 Cox L W Infertility A comprehensive programme Br J Obstet Gynaecol 82 2 1975
9 Drake T Tredway D Buchnan G Takaki N & Daane T Unexplained infertility a reappraisal Obstet Gynecol 50 644 1977
10 Peterson E P & Behrman S J Laparoscopy of the infertile patients Obstet Gynecol 35 363 1970
11 Jones G S Editorial comment Obstet Gynecol Survey 31 153 1976
12 Dodson K S Macnaughton M C & Coutts J R T Infertility in women with apparent ovulatory cycles II The effects of clomiphene treatment on the profiles of gonadotropins and sex steroid hormones in peripheral plasma Br J Obstet Gynaecol 82 615 1975
13 Editorial Antibodies to spermatozoa Br Med J 4 774 Oct 1976
14 Jones W R The use of antibodies developed by infertile women to identify relevant antigens I Karolinska Symposia on Research Methods in Reproductive Endocrinology 7th Symposium Immunological Approaches to Fertility Control 1974
15 Gemzell C Induction of ovulation with human gonadotropins J Reprod Med 18 155 1975
16 Royal College of General Practitioners of England Oral Contraceptives and Health Pitman London 1974

Submitted for publication July 27 1978

Carl Gemzell M D
Dept of Obst and Gyn
Downstate Medical Center
450 Clarkson Av
Brooklyn N Y 11 03
USA

Acta Obstet Gynecol Scand 58 147–152 1979

PREGNANCY COMPI ICATIONS FOLLOWING LEGALLY INDUCED ABORTION WITH SPECIAL REFERENCE TO ABORTION TECHNIQUE

E Obel

From the Department of Obstetrics and Gynaecology YA University of Copenhagen and the Department of Gynaecology Frederiksberg Hospital Copenhagen Denmark

Abstract A study of 576 pregnant women whose previ ous pregnancy had been terminated by legally induced abortion has shown that the rate of pregnancy and deliv ery complications could not be correlated with the interval between the abortion and the subsequent pregnancy nor with the gestational age at the time of abortion nor the number of previous induced abortions Neither was the abortion technique found to correlate with the frequency of complications in a subsequent pregnancy It was found however that more infants with a birth weight below 2 501 grams were born to women whose cervical canal during abortion had been dilated more than 12 mm and by wom en who had been submitted to recurettage The latter group also demonstrated a higher frequency of retained placenta or placental tissue

In 1972 a Hungarian study (Hungarian Central Statistical Office (5)) demonstrated a correlation be tween previous induced abortions and prematurity in such a way that the prematurity rate increased with the number of legally induced abortions Sev eral later studies have endeavoured to evaluate the me problem Harlap & Davies (3) von Lembrych (6) Pantelakis et al (9) Papavangelou et al (10) and the latest Richardson & Dixon (11) have dem onstrated an increased prematurity rate in women with previous induced abortions Daling & Emanuel (1) Furusawa & Koya (2) and Roth & Aoyama (12) could not demonstrate any such correlation Differ ences in the background of the group such as pari ty socio-economic status smoking habits and the method used for abortion may explain these incon sistent findings Obel (8) Hogue (4) examined the relationship between pregnancy outcome and the method and gestation of the preceding abortion but the sample of 87 patients was small

This paper will examine whether the interval be tween the induced abortion and the next pregnancy the abortion procedure adopted the extent of cervical dilatation acute abortion complications or the number of induced abortions influence the kind and number of complications in a subsequent preg nancy

The study has been supported by WHO the ma terial being part of WHO s multicenter trial Pro- spective study on the outcome of pregnancy fol lowing previous legally induced abortion

MATERIALS AND METHODS

The study included all women whose previous pregnancy was terminated by legal abortion registered during the period 1 April 1974 to 31 December 1975 for delivery at Rigshospitalet and at Frederiksberg Hospital in Copenhagen A total of 576 women were registered at their first application to the antenatal clinic All women were interviewed by specially employed and trained staff

The following data were collected age occupation education smoking habits medication during pregnancy possible diseases previous pregnancies and their out come the last type of contraception used whether the present pregnancy was planned and the date of the last menstrual period Obel (8 9)

From information provided by the patient we were able to obtain abortion records for 546 cases Eleven women had had the abortion abroad and in a further 19 cases the record could not be traced From these records the follow ing data on the original operation were extracted (*a*) Date and gestational age at operation (*b*) The technique used including the degree of dilatation of the cervix (in mm) (*c*) Immediate complications

We intended to interview all 576 women for a second time on or after 28 weeks of gestation and succeeded in doing so in 541 (94%) cases Information was collected on smoking habits medication exposure to X ray and ultrasound working conditions and complications of preg nancy The outcome of the pregnancy was later extracted from hospital records

The estimation of gestational age at delivery was based on the date of the last menstrual period as stated by the patient at the first interview and subject to inherent inac curacy

Patients with diabetes mellitus and twins were excluded from the analysis As most patients were not

A ta

Table I. Pregnancy and delivery complications in women whose previous pregnancy had been terminated by legally induced abortion with special reference to the interval between abortion and the subsequent pregnancy, gestational age at the abortion and the number of induced abortions

	Interval between legally induced abortion and indexed pregnancy						Gestation at abortion			
	<6 months		6–12 months		>12 months		Less than 13 weeks		13 weeks or more	
	No	%	No	%	No	%	No	%	No	%
Total number of patients	83		123		305		440		73	
Birthweight less than 2501 g	5	6.0	9	7.3	22	7.2	32	7.3	4	5.6
Gestation less than 37 weeks	7	9.1	12	10.5	21	7.5	38	9.7	6	9.5
Bleeding during pregnancy	19	22.9	35	28.5	65	21.2	104	23.6	17	23.3
Forceps or vacuum delivery	9	10.8	11	8.9	40	13.1	48	10.9	8	11.0
Breech delivery	0		2	1.6	5	1.6	5	1.1	0	
Caesarean section	11	13.3	14	11.4	32	10.5	43	9.8	13	17.8
Induction of labour	12	14.5	34	27.6	58	19.1	87	19.8	15	21.1
Second stage of labour 30 min or more	21	30.9	27	26.[illegible]	79	30.4	112	29.7	16	28.1
Third stage of labour 30 min or more	4	5.7	9	8.7	17	6.4	29	7.5	2	3.4
Retained placenta or placental tissue	3	3.6	11	8.9	22	7.2	32	7.3	3	4.1
Apgar score 1 min less than 8	7	8.6	13	10.7	31	10.3	37	8.5	8	11.4
Apgar score 5 min less than 8	2	2.5	2	1.7	5	1.7	7	1.6	1	1.4

* The difference is significant $p<0.05$
Patients where information is not available are excluded from the analyses of the relevent variable(s)

…d 15–20 weeks of gestation 67% before 20 weeks it is not possible to evaluate the frequency of spontaneous abortion. Spontaneous aborters are therefore excluded from the analysis.

Statistics

In the analysis the marginal distributions were tested by means of χ^2 test, and 5% was regarded as the significance level. When the expected number of the individual categories was lower than 5, Fischer's exact test was adopted and 2.5% regarded as the significance level.

RESULTS

After excluding diabetics and twin pregnancies 552 women were studied. Of theses 469 (85%) had had one and 83 (15%) two or more previous induced abortions.

In 511 women it was possible to determine the interval from the previous abortion to the last menstrual period. In 83 (16.2%) the interval was less than 6 months, in 123 (24.1%) from 6–12 months and in 305 (59.7%) the interval was more than 12 months.

The abortion technique employed at the termination of the previous pregnancy was recorded in 522 cases. In 415 (79.5%) suction termination was employed, 45 (8.6%) had their abortion performed by dilatation and curettage (D+C), 25 (4.8%) by intra-amniotic saline instillation, 10 (1.9%) by intra-amniotic prostaglandin instillation, 4 (0.8%) by hysterotomy, 17 (3.3%) by other methods, and 6 (1.2%) by extraamniotic prostaglandin instillation.

The gestational age at the time of induced abortion *could be determined for 513 women. In 440* (85.8%) the abortion was performed at 12 weeks of gestation or earlier.

The extent of cervical dilatation was recorded in 404 of 415 women (97.3%) who had been treated by suction termination. *In* 337 (81%) of these the abortion was performed at 12 weeks gestation or earlier. The cervix had been dilated more than 12 mm in 67 women (16.6%) and in 337 (83.4%) the cervix had been dilated 12 mm or less.

38 (9.2%) women treated by the suction method developed pelvic inflammatory disease complicating the operation, and in 21 (5.1%) recurettage had been necessary.

There was no correlation between the interval from the induced abortion to the indexed pregnancy and the frequency of pregnancy nor delivery complications (Table I). Neither was there any correlation between gestation at the time of induced abor-

Number of previous induced abortions			
One		Two or more	
No	%	No	%
69		83	
30	6 4	9	10 8
34	8 1	12	16 7
04	22 2	23	27 7
54	11 5	8	9 6
6	1 3	1	1 7
51	10 9	14	16 9
96	20 5	14	16 9
18	29 5	31	37 3
3	7 8	2	3 0
31	6 6	8	9 6
42	9 1	9	11 1
6	1 3	4	5 0

tion and the complications indicated in the indexed pregnancy (Table I)

The number of pregnancies ending before 37 weeks gestation was doubled in women with two or more previous induced abortions when compared with women with only one previous induced abortion The number of infants with birth weight below 2 501 g was not significantly increased

Table II indicates the correlation between the abortion technique and some immediate abortion complications and the complications in the indexed pregnancy An important difference between D & C and suction is the degree of dilatation of the cervix In suction abortion dilatation of the cervix exceeded 12 mm in nearly 15% of cases compared with 60% for D & C Dilatation beyond 12 mm or recurettage was associated with an increased frequency of low birth weight (less than 2 501 g) (Table II) Short gestation (less than 37 weeks) occurs significantly more often following D & C than after suction termination but the difference in frequency of low birth weight infants was not significant

An increased number of infants of low birth weight (below 2 501 g) was found among women in whom the cervical canal had been dilated more than 12 mm and among women who had been treated with récurettage (Table II) Table II also illustrates the frequency of 3rd stage complications Retained placenta and prolonged 3rd stage (more than 30 min) was more common in women with a history of recurettage Recurettage was also followed by a significant increase in both low birth weight infants and an Apgar score at five minutes of less than 8

The recorded descriptive variables collected at the first and second interviews were tested for evidence of differences between the groups Only between the group of women with one previous induced abortion and the group with two or more induced abortions did the tests reveal differences correlated with low birth weight infants and/or short gestation Obel (7) 15 6% of the women with one induced abortion had delivered more than once previously whereas the equivalent figure in women with more than one previous induced abortion was 33 7% Thus women with more than one previous induced abortion were characterized by higher parity this fact was expected to cause a higher frequency of infants with low birth weight and of deliveries before 37 weeks of gestation Obel (7)

DISCUSSION

These results show no association between unfavourable outcome of the indexed pregnancy and the time interval from the induced abortion There is therefore no support for the theory that the harmful effects of an induced abortion fade as the uterine lesion heals

Hogue (4) found no difference in the number of low birth weight infants (<2 501 g) between first trimester aborters and second trimester aborters Consistent with this finding we could find no difference in the frequency of low birth weight infants (less than 2 501 g) nor of other pregnancy complications in indexed pregnancies which followed a first as compared with a second trimester abortion This is of particular importance because of the increasing use in for example Denmark of second trimester abortion occurring as a result of improved prenatal diagnosis of congenital anomalies Neither was there an excess of complications in the succeeding pregnancy in aborters treated with other methods when compared with suction termination (Table II) The former group primarily comprised abortion procedures used after 12 weeks gestation it in

Table II. Pregnancy and delivery complications in women whose previous pregnancy had been term... legally induced abortion with special reference to abortion technique, extent of cervical dilat... complications as pelvic inflammatory disease and recurettage

	Abortion procedure								Abortion done by suction			
	Suction		Dilatation and curettage (D+C)		Suction		Procedures other than suction and D+C		Dilatation 12 mm or less		Dilatation 13 mm or more	
	No	%	No	%	No	%	No	%	No	%	No	%
Total number of patients	415		45		415		62		337		67	
Birthweight less 2 501 g	28	6 7	3	6 7	28	6 7	6	9 8	18	5 3	9	13 4
Gestation less than 37 weeks	29	7 8	8	17 8	29	7 8	13	13 6	2_	7 3	6	11 1
Bleeding during pregnancy	97	23 4	12	26 1	97	23 4	14	16	79	23 4	16	19
Forceps or vacuum delivery	47	11 3	4	8 9	47	11 3	6	9 7	41	1	6	9
Breech delivery	5	1 2	0		5	1 2	0		5	1 5	0	
Caesarean section	42	10 1	7	15 6	42	10 1	10	16 1	33	9 8	8	11 9
Induction of labour	87	21 0	11	18 3	87	21 0	7	15	75	22 3	10	14 9
Second stage of the delivery more than 30 min	104	29 5	10	26 3	104	29 5	14	8 6	83	30 6	13	41
Third stage of the delivery more than 30 min	24	6 6	3	7 9	24	6 6	4	8 0	21	7 1	3	5
Retained placenta or placental tissue	29	6 9	1	2	29	6 9	5	8 1	25	7 4	1	4
[illegible] 1 min [illegible] than 8	33	8 1	3	6 5	33	8 1	9	15 3	8	8 4	4	6
[illegible] score 5 min less than 8	5	1 2	1	2	5	1		3 4	4	1	0	

The difference is significant $p<0.01$
Patients where information is not available are excluded from the analyses of the relevant variable(s)

cluded 41 (66%) who had been treated with intrauterine saline or prostaglandin

Short gestation (less than 37 weeks) occurred twice as often in women who had had multiple induced abortions as in those with a history of only one (Table I). In spite of this there is no equivalent rise in the frequency of low birth weight infants or of other complications. The interpretation is complicated by the fact that the women with multiple abortions also tend to be of higher parity than those with only one. A fact which would be expected to cause an increased rate of deliveries before 37 weeks of gestation as well as of infants with low birth weight. Obel (8). In consequence of this fact combined with the inaccuracy connected with the calculation of gestational age, based on last menstrual period only, this study cannot prove a cumulative effect of two or more abortions

This study tried to evaluate if the type and frequency of complications in the indexed pregnancy were correlated with the abortion technique adopted. Hogue (4) only studied the rate of prematurity and could not show any correlation with the abortion technique; this is consistent with the present study which does not demonstrate any correlation between abortion technique and low birth weight. Short gestation, however, was more frequent in women treated with dilatation and curettage than with suction. An isolated finding which should be considered with reservations as already indicated

The lesion of the uterine cervix caused by the operation presumably corresponds with the extent of the dilatation. Women whose cervical canal had been dilated more than 12 mm had a significant increased frequency of low birth weight infants, but at the same time the frequency of deliveries before 37 weeks of gestation was not increased. There was no correlation between other complications and the extent of dilatation. As no significant difference

complications mentioned are increased in a subsequent pregnancy

ic inflamatory ease				Abortion complicated by recurettage			
o		Yes		No		Yes	
o	%	No	%	No	%	No	%
7		38		394		21	
7	7 ?	1	2 6	?3	4 6	5	?3 8
6	7 8	3	8 8	26	7 4	3	15 8
0	23 7	7	18 4	89	?2 6	8	38 1
3	11 4	4	10 5	45	11 4	2	9 5
4	1 1	1	2 6	5	1 3	0	
10	10 6	2	5 3	39	9 8	8	11 9
3)	21 2	7	18 4	86	21 8	2	9 6
96	30 2	8	22 9	98	?9 3	6	33 3
??	6 7	2	5 7	?0	5 8	4	?2 2
6	6 9	3	7 9	3	5 8	6	28 6
30	8 1	3	8 1	30	7 7	3	14 3
5	1 3	0		3	0 8	?	9 5

could be demonstrated in background variables of the patients compared the correlation between di l tation and low birth weight infants supports the theory that dilatation beyond 12 mm increases the risk of low birth weight in a subsequent pregnancy

When an induced abortion was followed by re curettage there was a significant increase in the complications in the succeeding pregnancy although the presence of pelvic inflammation alone did not contribute The effect was seen to be an increased incidence of low birth weight and low Apgar scores after five minutes (these two effects probably being related) and complications of the 3rd stage of labour related to retained placenta or placental tissue suggesting that damage may have occurred to the endometrium These findings can not be explained by differences in the background variables of the two groups These results indicate that either the factors necessitating récurettage or the operation itself cause such lesions that the

CONCLUSION

This study does not support the theory that the interval between legally induced abortion and the next pregnancy length of gestation at the abortion procedure the number of induced abortions or the abortion technique influence the frequency of preg nancy complications in a subsequent pregnancy Only among women whose cervical canal had been dilated more than 12 mm and among women treated with recurettage was there an increased risk of delivering infants with birth weight below 2501 grams The latter group also demonstrated in creased risk of retained placenta or placental tissue

ACKNOWLEDGEMENT

This investigation received financial support from the World Health Organization as well as from Danish Medi cal Research Council

REFERENCES

1 Daling J R & Emanuel I Induced abortion and subsequent outcome of pregnancy Lancet *II* 170 1975
? Furusawa J & Koya T The influence of artificial abortion on delivery *In* Harmful Effects of Induced Abortion (ed Y Manyama) p 74 Tokyo 1966
3 Harlap S & Davies A M Late sequelae of induced abortion Complications and outcome of pregnancy and labor Am J Epidemiol *10?* 217 1975
4 Hogue C J Low birthweight subsequent to induced abortion Am J Obstet Gynecol *123* 675 1975
5 Hungarian Central Statistical Office The effect of the number of abortions on premature births and perinatal mortality in Hungary Budapest 1972
6 von Lembrych S Schwangerschafts Geburts und Wochenbettverlauf nach kunstlicher Unterbrechung der ersten Gravidität Zentralbl Gynaekol 94 164 197?
7 Obel E B Pregnancy complications following le gally induced abortion (To be published)
8 Obel F B Pregnancy complications following le gally induced abortion An analysis of the composi tion of the population examined with special reference to factors correlated with prematurity (To be pub lished)
9 Pantelakis S N Papadimitriou G C & Doxua dush S A Influence of induced and spontaneous abortions on the outcome of subsequent pregnancies Am J Obstet Gynecol *116* 779 1973

10 Papavangelou G Vrettas A S Papadotas C & Alexiou D The effect of spontaneous and induced abortion on prematurity and birthweight Br J Obstet Gynecol 80 418 1973
11 Richardson J A & Dixon G Effects of legal termination of subsequent pregnancy Br Med J 1 1303 1976
12 Roth L H & Aoyama H Induced abortion and its sequelae Prematurity and spontaneous abortion J Obstet Gynecol 120 868 1974

Submitted for publication April 24 1978

Erik B Obel M D
Ved Höjmosen 13 8
2970 Hörsholm
Denmark

Acta Obstet Gynecol Scand 58 153–161 1979

ULTRASOUND DIAGNOSIS OF FETAL ABNORMALITIES IN MULTIPLE PREGNANCY

A Kurjak and V Latin

From the Ultrasonic Center of the Department of Obstetrics and Gynecology the Medical Faculty University of Zagreb Yugoslavia

Abstract Over a period of four years 41 cases of abnormal multiple pregnancies were diagnosed successfully by ultrasound These include several rare combinations of abnormalities The most frequent was a normal pregnancy and a synchronous blighted ovum Others were twin blighted ova blighted ovum and missed abortion missed abortion in both gestational sacs two embryonic echoes with the development of only one baby normal fetus and an anencephalic twin normal fetus and fetus papyraceous and triplets with two fetuses papyraceous The results suggest that one or more gestational sacs may be resorbed during pregnancy without any adverse effect on the coexisting normal fetus From a practical point of view it is important to be aware of these possibilities before giving the final diagnosis of multiple pregnancy to the patient The more diagnostic ultrasound is used in obstetrics the more rare abnormalities associated with multiple pregnancies will be revealed

The successful use of diagnostic ultrasound in the detection of multiple pregnancies was first described in 1958 by Donald et al (1) Since that time numerous authors have confirmed that ultrasound is the method of choice in the diagnosis and assessment of multiple pregnancies (4) One of the important advantages of this diagnostic tool is its capability of examining early multiple pregnancy and of obtaining information which might otherwise be lost Before the extensive application of ultrasound there was little information available on the incidence and nature of abnormalities in multiple pregnancies Some recent ultrasonic papers however have made an important contribution to understanding these unusual findings better (8 12)

It is the purpose of this paper to describe and illustrate several rare abnormalities in multiple pregnancy detected by ultrasound during early and late pregnancy

PATIENTS AND METHODS

The ultrasonic diagnosis of multiple pregnancy was made by thoroughly examining every pregnancy from one side of the uterus to the other with multiple closely spaced section scans In the early part of the first trimester multiple gestation sacs are demonstrable but later two or more fetal echo complexes can be clearly identified Special attention was given to the detection of fetal heart movements within each fetal echo Further verification was made by identifying asynchronous fetal movements using the real time ultrasonic machine These are particularly valuable diagnostic aids when the gestational sacs are no longer visible as ring echoes As a normal multiple pregnancy we accepted the pregnancy in which two or more distinct fetal echoes with fetal heart movements within each fetus were identified and which continued to grow normally In a later pregnancy this was confirmed by the demonstration of two or more fetal heads and bodies which continued to have normal development Any other findings of multiple pregnancy were considered abnormal Before making the final diagnosis of abnormality particular attention was paid to the slight possibility of human error and especially to the possibility of artefacts In all of our patients therefore the diagnosis was confirmed after a repeat examination in an interval of one to two weeks

The classification of abnormal early multiple pregnancy was the same as described by Robinson (11) for singleton pregnancies The apparatus used were Diasonograph NE 4107 with the gray scale and ADR real time model 2130

RESULTS

During the last four years over 20000 pregnant women have been examined in our Ultrasonic Center Among them we found 41 cases of abnormal multiple pregnancies which were classified in the following groups blighted ovum/normal pregnancy (20 patients) blighted ovum/blighted ovum (nine patients) blighted ovum/missed abortion (two patients) missed abortion/missed abortion (two patients) two embryonic echoes with development and delivery of only one baby (three patients) normal fetus/anencephalic fetus (one patient) normal fetus/fetus papyraceous (two patients) and normal fetus/two fetuses papyraceous (two patients)

Blighted ovum/normal pregnancy (20 patients)

Our most frequent finding was double gestational sacs in which the smaller one was anembryonic and



Fig 1 Normal pregnancy of nine weeks in right gestational sac and coexisting blighted ovum in left Scale 2 5

no longer visible at repeated ultrasonic examinations Illustrative cases are shown on Figs 1 to 4 ineteen of these patients had a normal baby and y one twin pregnancy ended in spontaneous ion

Blighted ovum/blighted ovum
(nine patients)

Two of the twin blighted ova from this group were hydatidiform moles The first patient was seen at 11 weeks of amenorrhea We suspected twin bligh ova on the basis of the ultrasonic findings (Fig Two weeks later the diagnosis was confirmed by the obvious regression of both sacs (Fig 6) and the typical appearance of molar tissue Interestingly a hormonal and clinical findings at that time we normal The next ultrasonic examination ten days later verified the diagnosis of hydatidiform mole and the pregnancy was terminated electively (F 7)



Fig 2 The same pregnancy three weeks later Fetal crown rump length is 55 mm with pos ve fetal heart movements Second gestational sac completely d sappea e Scale 5 5



Fig 3 Two gestational sacs at seven weeks Embryonic echo clearly visible in lower sac Scale ? 5

Blighted ovum/missed abortion
(two patients)

Both patients from this group were examined first at seven weeks amenorrhea and double sacs were clearly defined In one of the patients embryonic echoes with fetal heart movements were identified in one gestational sac while the second sac was empty At the second ultrasonic examination three weeks later the typical ultrasonic picture of missed abortion was found and the pregnancy was terminated electively (Fig 8)

Missed abortion/missed abortion
(two patients)

In both of these patients two gestational sacs with live embryos were observed at the first examination During the second examination there were no signs of fetal life and the diagnosis of missed abortion was confirmed histologically



Fig 4 The same pregnancy at 13 weeks No evidence of second gestational sac A healthy baby delivered at term Scale 5 5



Fig. 5. Twin blighted ova at 11 weeks of gestation. Scale 3 : 5.

Two embryonic echoes with development and delivery of one baby (three patients)

all three patients the diagnosis of live twins was on the initial ultrasonography between eight to 12 weeks of amenorrhea. At repeat examinations two to four weeks later there was only one left. A typical case is illustrated on Figs. 9 and 10. The patient P. B., 22-year-old II para, had the first ultrasonic examination at 11 weeks of amenorrhea. Two fetal echoes were recorded and documen by polaroid photographs. The diagnosis was confirmed two weeks later by findings of asynchro spontaneous fetal movements from two fetus which grew normally during the interval betwe two repeated examinations. At 18 week amenorrhea only one normal baby was found th other had disappeared without vaginal bleed The development of the first baby was normal a at the expected date of delivery the patient ga



Fig. 6. The same case two weeks later with obvious regression of both gestational sacs. Scale 3 : 4.



Fig 7 Typical appearance of molar tissue in the same case Scale 2 5

birth to a normal weighing healthy child Placenta and membranes were complete there were no signs of the second fetus

Normal fetus/anencephalic twin
(one patient)

This unusual finding was described and illustrated elsewhere (7)

Normal fetus/two fetuses papyraceous
(two patients)

One of the two cases is illustrated on Figs 11 and 12 At 20 weeks of amenorrhea twins were discovered by the findings of two fetal heads At 36 weeks one fetus was normal while the other was visualized as a soft tissue mass in the uterine fundus At 38 weeks the patient was delivered of a healthy boy and a fetus papyraceous

Normal fetus/two fetuses papyraceous
(two patients)

We had a very interesting case of triple pregnancy diagnosed at 18 weeks which is illustrated on Fig 13 Fifteen weeks later the patient came for a second examination and only one fetus was found (Fig



Fig 8 Empty gestational sac on left and missed abortion on right Scale ? 5



Fig 9 Twins at 11 weeks of amenorrhea described in text Scale = 5

(4) In the uterine fundus however there were two white rings and a soft tissue mass The patient was examined by an experienced radiologist and the X ray missed showing any abnormalities associated with the one normally growing baby Labour was spontaneous and a healthy boy weighing 3 120 grams was delivered After a normal III stage exploration of the uterus was performed and twins with a common placenta were removed (Fig The pathologist s estimation of fetal age was a twenty weeks two babies having died two w after the first ultrasonic examination This il tive case shows the significant advantage ultrasound as compared with X ray Very re we had another similar case in which X ray missed giving a correct diagnosis

DISCUSSION

The majority of reports agree that there is i creased incidence of malformations in mu pregnancies (9) Henricks found that amon twins the anomaly rate was 10 6 compared 3 3% for all births (3) In an analysis of consec births from 24 centers throughout the w Stevenson et al reported a higher rate of cong malformations among twins than in singletons

Several of the rare abnormalities can be det by ultrasound First of all the presence of than one gestational sac need not be assoc necessarily with the development of more tha fetus From our results it is obvious that o more gestational sacs apparently may be reso during pregnancy without having an adverse e on the coexisting normal fetus From the pra point of view it is important to stress that vaginal bleeding is the only complication w sometimes occurs with the regression of a bl ovum In 1973 Helmann et al published a det

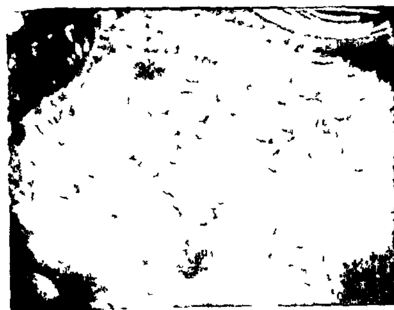


Fig 10 The same patient a 18 weeks Only one n m l baby f with the placenta p ... Scale 3 5



Fig 11 Two fetal heads in twins diagnosed at ?0 weeks Scale 4 5

report on this phenomenon Of 22 pregnant women with two gestational sacs seen during early pregnancy 14 aborted three were delivered of a single infant and only five had twins (2) Kohorn & Kaufmann (5) and Reinold (10) stress also that the presence of a double sac is not necessarily consistent with the development of two fetuses nor is it to be regarded as a sign of the termination of a pregnancy In a recent paper Robinson (12) described 30 patients in whom twin conception was discovered by ultrasound during the first trimester of pregnancy Of these 30 patients 14 gave birth to twins Eleven of the remaining 16 patients were found to have a normal pregnancy and a coexistent blighted ovum Of the last five patients four were diagnosed as having twin blighted ova and one a blighted ovum and a missed abortion He concludes that the incidence of twin conceptions is higher than the commonly accepted figure of one in 80 We agree with his statement

We believe that these findings are important for many reasons Some of them we have already de



Fig 12 The same patient at 36 weeks of pregnancy A white ring on left which represents head of the fetus papyraceous Head of normally growing twin on right Scale 4 5



Fig 13 Triplets diagnosed at 18 weeks of pregnancy Scale ? 5

scribed For most ultrasonographers it is important to know such information before giving the final diagnosis of a multiple pregnancy to the patient

Finally it must be emphasized that the more c ultrasound is used in obstetrics the more abnormalities associated with multiple preg ies will be revealed

REFERENCES

1 Donald I MacVicar J & Brown T G Investigation of abdominal masses by pulsed ultrasound Lancet *1* 1188 1958

2 Hellman L M Kobayashi M & Cromb E Ultrasonic diagnosis of embryonic malformation Am J Obstet Gynecol *115* 615 1973

3 Hendricks C H Twining in relation to birth weight mortality and congenital anomalies Obstet Gynecol *27* 47 1966

4 Jouppila P Kaupilla A Koivisto M Moilanen I & Ylikorkala O Twin pregnancy The role of act management during pregnancy and delivery Acta Obstet Gynecol Scand Suppl *44* 13 1975

5 Kohorn E I & Kaufmann M Sonar in the first trimester of pregnancy Obstet Gynecol *44* 473 1974

6 Kurjak A The antenatal diagnosis of fetal malformations and abnormalities by ultrasound *In* Ultrasound in Medicine (ed E Kazner M de Vlieger & H



Fig 14 Fifteen weeks later only one baby Scale 2 5



Fig 15 The same patient Twins with common placenta after removal from uterus

Muller) p 304 Excerpta medica Amsterdam and Oxford 1975
Kurjak A Ultrasonic detection of fetal malformation and abnormalities *In* Handbook of Clinical Ultrasound (ed A Kratochwil) John Wiley and Sons New York 1978 p 189
8 Kurjak A *Direct ultrasonic diagnosis of fetal* abnormalities *In* Recent Advances in Ultrasound Diagnosis (ed A Kurjak) Excerpta medica Amsterdam 1978 (in press)
9 MacGillivray I Malformations and other abnormalities in twins *In* Human Multiple Reproduction (ed I MacGillivray P P S Nylander & G Gorney) p 165 Saunders London 1975
10 Reinold E Ultrasonics in Early Pregnancy p 95 S Karger Basel 1976
11 Robinson H The diagnosis of early pregnancy failure by sonar Br J Obstet Gynaecol *82* 849 1975
12 Robinson H Sonar evidence of early pregnancy failure in patients with twin conceptions Br J Obstet Gynaecol *84* 22 1977
13 Stevenson A C Johnston H A Stewart M I & Goldin D R Congenital malformations A report of a study on a series of consecutive births in 24 centers *Bull WHO 34 1–127 1966*

Submitted for publication Febr 22 1978

Asim Kurjak M D D Sc
School of Medical Ultrasound
Medical Association of Croatia
Petrova ul 13
41000 Zagreb
Yugoslavia

ANNOUNCEMENT

IX WORLD CONGRESS OF GYNECOLOGY AND OBSTETRICS IN TOKYO

October 25–31, 1979

NEW TOUR ALTERNATIVES

Travel Arrangement No 1
Scandinavia – Tokyo – Scandinavia
23 10–3 11 1979
Takanawa Prince Hotel in Tokyo
The cost of this arrangement will be approximately Sw Crs 7 250

Travel Arrangement No 2
Scandinavia – Tokyo – China – Hong Kong – Delhi – Nepal – Scandinavia
23 10–13 11 1979
Keio Plaza Hotel in Tokyo
Tour conductor Professor Ingemar Joelsson
The cost of this arrangement will be approximately Sw Crs 11 990

Travel Arrangement No 3
Scandinavia – Tokyo – Bali – Sydney – Christchurch – Tahiti – San Francisco – Scandinavia
23 10–18 11 1979
Keio Plaza Hotel in Tokyo
Tour conductor Professor John Philip
The cost of this arrangement will be approximately Sw Crs 17 900

Detailed program can be requested from **World Tourist Travel Bureau** Bredgade 19 DK 1260 Copenhagen K Denmark Phone 01/151945, Gorm Pedersen/Niels Erik Christensen

These tours are planned by World Tourist Travel Bureau in Denmark in close cooperation with *Japan Travel Bureau* (the official agent of the congress) and *SAS – Globetrotter*





Acta Obstet Gynecol Scand 58 163–167 1979

PLACENTA AS AN INDICATOR OF FETAL POSTNATAL PROGNOSIS

K Lauslahti and S Ikonen

From The Department of Pathology and Pediatrics Tampere Central Hospital Tampere Finland

Abstract 468 placentas were studied microscopically and by gross examination Velamentous insertion of the umbilical cord placenta circumvallate retroplacental hematoma in connection with ablation of the placenta and cord prolapse were found to be causative factors in asphyxia of the newborn The increased placental weight was characteristic in maternal diabetes hepatosis and sometimes in cases of infant malformations and specific inflammations So-called embryonal persistence was often found histologically in these changes Small fibrous placentas and those with ramification defects were commonly encountered among cases of toxemia and prolonged gestation Microscopical placental maturation defects were not indicative of the fetal condition Thus only the changes found at gross examination appeared to be a significant indicator of the fetal prognosis

Examination of the placenta is a common problem for obstetricians pediatricians and pathologists In particular the significance of the findings as a characteristic of the fetal prognosis is unclear Various models have been presented for the examina n of the placenta and fetal outcome (2 3 5 15 3) On the other hand traces of some maternal diseases have been found in the placenta or the fetus (4 6 10 12 13 14 22 25) It has also been noted that certain malformations placental implantation defects and blood circulation defects may affect the placenta and the newborn (9 11 26)

In this study the conventional pathological examination of the placenta was extended and the placenta analysed to find changes that may prove significant characteristics of fetal prognosis

MATERIAL AND METHODS

The present material is based on a total of 4077 live births in 1973 at the Tampere Central Hospital Finland 468 placentas from these births were sent to the Department of Pathology for examination On the recommendation of the obstetricians pediatricians and occasionally midwives the placentas were examined in all cases of maternal diseases e g hypertension toxemia diabetes mellitus and hepatosis and furthermore in cases of asphyctic infants (Apgar score ≤7) and infants taken to the newborn intensive care unit (ICU)

First the placentas were weighed whole and then without the fetal membranes and umbilical cord This gave the true placental weight The relative placental weight (RPW) was obtained from the formula

$$\frac{100 \times \text{pure placental weight}}{\text{fetal weight}}$$

The gross examination was carried out in accordance with Benirschke s (3) and Kloos s (16) checking list This examination gave information primarily about the lesions of the placental implantation time (before 20th week of gestation) (4 26) and about blood circulation defects

In the microscopical examination the material was mainly classified according to the placental maturation defects (17 20) Four samples of each placenta were taken for microscopical examination one of the umbilical cord one of the fetal membranes and one of the central part and one of the edge of the placenta

The microscopical findings were classified in three main groups

1) Group I consisted of placentas in which the placental findings were as described by Kloos & Vogel (17) persistent embryonal villus structure arrest of ramification or *discordant retarded villus structure This group we called* embryonal persistence placentas A common feature was tall edemic villi containing few blood vessels The stroma of the villi was loose and so-called Hofbauer cells were found The deficient chorionic epithelium surrounding the villi was imperfectly differentiated

2) Group II consisted of placentas with defects which Kloos & Vogel (17) characterized as dissociated maturation defect and frank differentiation defect of rami villisi These we called villous ramification defect placentas Dilatation and hyperemia of the terminal villous blood vessels were common and fibrous growth in the villous stroma was often present

3) Group III consisted of the retarded structures in which villous ramification had been checked to some extent and reticular connective tissue metaplasia was found in the mesenchyma of the villi Kloos & Vogel (17) described this as a concordant retarded villous structure

ANNOUNCEMENT

IX WORLD CONGRESS OF GYNECOLOGY AND OBSTETRICS IN TOKYO

October 25–31 1979

NEW TOUR ALTERNATIVES

Travel Arrangement No 1
Scandinavia – Tokyo – Scandinavia
23 10–3 11 1979
Takanawa Prince Hotel in Tokyo
The cost of this arrangement will be approximately Sw Crs 7 250

Travel Arrangement No 2
Scandinavia – Tokyo – China – Hong Kong – Delhi – Nepal – Scandinavia
23 10–13 11 1979
Keio Plaza Hotel in Tokyo
Tour conductor *Professor Ingemar Joelsson*
The cost of this arrangement will be approximately Sw Crs 11 990

Travel Arrangement No 3
Scandinavia – Tokyo – Bali – Sydney – Christchurch – Tahiti – San Francisco – Scandinavia
23 10–18 11 1979
Keio Plaza Hotel in Tokyo
Tour conductor Professor John Philip
The cost of this arrang ment will be approximately Sw Crs 17 900

Detailed program can be requested from **World Tourist Travel Bureau** Bredgade 19 DK 1260 Copenhagen K Denmark Phone 01/151945 Gorm Pedersen/Niels Erik Christensen

These tours are planned by World Tourist Travel Bureau in Denmark
in close cooperation with
Japan Travel Bureau (the official agent of the congress) and *SAS – Globetrotter*





Acta Obstet Gynecol Scand 58 163–167 1979

PLACENTA AS AN INDICATOR OF FETAL POSTNATAL PROGNOSIS

K Lauslahti and S Ikonen

From The Department of Pathology and Pediatrics
Tampere Central Hospital Tampere Finland

Abstract 468 placentas were studied microscopically and by gross examination Velamentous insertion of the umbilical cord placenta circumvallate retroplacental hematoma in connection with ablation of the placenta and cord prolapse were found to be causative factors in asphyxia of the newborn The increased placental weight was characteristic in maternal diabetes hepatosis and sometimes in cases of infant malformations and specific inflammations So-called embryonal persistence was often found histologically in these changes Small fibrous placentas and those with ramification defects were commonly encountered among cases of toxemia and prolonged gestation Microscopical placental maturation defects were not indicative of the fetal condition Thus only the changes found at gross examination appeared to be a significant indicator of the fetal prognosis

Examination of the placenta is a common problem for obstetricians pediatricians and pathologists In particular the significance of the findings as a characteristic of the fetal prognosis is unclear Various models have been presented for the examination of the placenta and fetal outcome (2 3 5 15 23) On the other hand traces of some maternal diseases have been found in the placenta or the fetus (4 6 10 12 13 14 22 25) It has also been noted that certain malformations placental implantation defects and blood circulation defects may affect the placenta and the newborn (9 11 26)

In this study the conventional pathological examination of the placenta was extended and the placenta analysed to find changes that may prove significant characteristics of fetal prognosis

MATERIAL AND METHODS

The present material is based on a total of 4077 live births in 1973 at the Tampere Central Hospital Finland 468 placentas from these births were sent to the Department of Pathology for examination On the recommendation of the obstetricians pediatricians and occasionally midwives the placentas were examined in all cases of maternal diseases e g hypertension toxemia diabetes mellitus and hepatosis and furthermore in cases of asphyctic infants (Apgar score ≤7) and infants taken to the newborn intensive care unit (ICU)

First the placentas were weighed whole and then without the fetal membranes and umbilical cord This gave the true placental weight The relative placental weight (RPW) was obtained from the formula

$$\frac{100 \times \text{pure placental weight}}{\text{fetal weight}}$$

The gross examination was carried out in accordance with Benirschke s (3) and Kloos s (16) checking list This examination gave information primarily about the lesions of the placental implantation time (before 20th week of gestation) (4 26) and about blood circulation defects

In the microscopical examination the material was mainly classified according to the placental maturation defects (17 20) Four samples of each placenta were taken for microscopical examination one of the umbilical cord one of the fetal membranes and one of the central part and one of the edge of the placenta

The microscopical findings were classified in three main groups

1) Group I consisted of placentas in which the placental findings were as described by Kloos & Vogel (17) persistent embryonal villus structure arrest of ramification or discordant retarded villus structure This group we called embryonal persistence placentas A common feature was tall edemic villi containing few blood vessels The stroma of the villi was loose and so-called Hofbauer cells were found The deficient chorionic epithelium surrounding the villi was imperfectly differentiated

2) Group II consisted of placentas with defects which Kloos & Vogel (17) characterized as dissociated maturation defect and frank differentiation defect of rami villisi These we called villous ramification defect placentas Dilatation and hyperemia of the terminal villous blood vessels were common and fibrous growth in the villous stroma was often present

3) Group III consisted of the retarded structures in which villous ramification had been checked to some extent and reticular connective tissue metaplasia was found in the mesenchyma of the villi Kloos & Vogel (17) described this as a concordant retarded villous structure

Table I. *Duration of the pregnancy in 468 cases*

Weeks of pregnancy	Pathological placentas (no.)	Normal placentas (no.)	Total No.	Total %
20–31	20	6	26	6
32–37	51	31	82	18
38–42	192	123	315	67
over 42	36	9	45	9
Total	299	169	468	100

Table II. *RPW and the pathological placental findings*

Placental findings	No.	RPW Below 11%	RPW 11–17%	RPW Over 17%
Normal	169	11	148	10
Embryonal persistence	54	–	22	32
Ramification defects	51	11	38	2
Fibrosis	73	32	38	3
Retardation	41	2	32	7
Inflammation	49	3	35	9
Velamentous insertion	12	–	11	1
Placenta circumvallate	13	–	11	2
Ablation of placenta	9	1	6	2
Cord prolapse	2	–	2	–
	468	60	340	65

RESULTS

299 (64%) out of the 468 placentas were pathological. Duration of pregnancy is given in Table I. Only 25% of the infants delivered before the 32nd week of gestation had a normal placenta. Ablation of the placenta in particular, but also inflammatory changes in the placenta, seemed to have a close connection with premature births. There were many cases of small fibrous placentas among the premature births. Of those born between 32 and 37 weeks of gestation nearly 50% were normal infants with large placentas in which embryonal persistence was often found constituted a noteworthy proportion. In this group there were also numerous inflammatory changes. A variety of placental changes were seen in the group of infants born after the 42nd week of gestation. Small fibrous placentas were found mostly in this group.

The classification of the relative placental weights (RPW) is according to Little (20). Three significant RPW groups emerged (Table II). According to the RPWs less than 11% of the small placentas were fibrotic, in most cases those of prolonged gestation. Microscopically ramification defects were frequent. Most of large placentas exceeding 17% showed embryonal persistence. Table II and III presented the relationship between the placental findings and the maternal diseases during gestation. The most important changes seen at gross examination were implantation defects such as velamentous insertion of the umbilical cord, placenta extrachoriale (placenta circumvallate), umbilical cord prolapse and signs of premature detachment of the placenta. Both placenta circumvallate and ablation were found to cause vaginal hemorrhage before delivery.

According to the microscopical classification (Table IV), embryonal persistence was particularly frequent in cases of maternal diabetes, hepatosis and in connection with specific inflammations such as toxoplasmosis and listeriosis. A large embryonal persistence placenta was found in one of two malformed infants. Ramification defects were most marked in the placentas of toxemic mothers. Stromal fibrosis was found in the placentas of both toxemic mothers and cases of prolonged gestation. The microscopical picture of retardation revealed characteristic metaplastic connective tissue in cases

Table III. *Gross examination findings in relation to maternal diseases*

Placenta findings	Maternal diseases: Hepatogestosis	Toxaemia	Bleeding during delivery	Non specific inflammation
Velamentous insertion (12)	1	–	1	1
Placenta circumvallate (13)	1	1	6	1
Ablation (9)	–	–	7	–
Cord prolapse (2)	1	1	–	–

Table IV *Microscopical placenta findings in relation to maternal diseases*

Disease	Placental findings					
	Normal	Embryonal persistence	Ramification defects	Fibrosis	Retardation	Inflammation
Diabetes	9	*7*	1	–	1	–
Hepatogestosis	5	6	–	–	4	–
Toxaemia	15	2	*11*	*8*	3	–
Prolonged gestation	9	1	–	*25*	3	3
Bleeding during delivery	3	1	1	?	–	–
Anaemia	2	–	–	*1*	–	*1*
Blood group incompatibility	2	–	–	–	–	–
Malignant disease	1	–	–	–	–	–
Nonspecific inflammation	12	–	–	2	1	
Toxoplasmosis	–	2	–	1	–	1
Listerosis	–	1	–	–	–	1
Malformation of infant	1	*4*	1	1	1	1

of hepatosis and prolonged gestation and occasionally in cases of toxemia

Examination of the placental findings in asphyctic newborns (Table V) revealed the implantation defects such as velamentous insertion of the umbilical cord and cord prolapse and the signs of ablation of the placenta to be significant causes of asphyxia In these groups the infant was asphyctic in over 50% of the cases

No special characteristics relevant to asphyxia emerged from the classification of the microscopically examined placentas The groups of microscopically defective placentas had as many asphyctic infants as that of normal placentas

DISCUSSION

The present material consisted of 468 (about 12%) placentas from 4077 deliveries 169 were normal and 299 pathological Thus in about 7% of the total number of births the placenta was pathological The checking list used for gross examination proved useful mainly in detecting implantation defects malformations and blood circulation defects (4 ?6) The grouping of the microscopic findings was determined by the author s own classification (?0) based on the following Hellman & Hertig (13) Hormann (14) Doring & Kloos (6) Kouvalainen et al (18) Essbach (7) Frank (10) and Vogel (25 26)

Foss & Vogel (8) found implantation defects (before ?0th week of gestation) in 75% of their placental material and placental defects in 96% For the infants however these were of clear clinical significance in only a few cases Aladjem et al (2) presented their own placental scoring system for evaluating the adaptation of the newborn to extrauterine life Scott & Jordan (23) also had their own scoring system with seven main parameters of the placenta for diagnosing placental insufficiency

In the present study only the placental findings showing clinical significance are presented For example the present material included one case of a single artery of the umbilical cord which had no clinical significance although other malformations are often seen in these infants (11) Similarly placental infarctions were found particularly in cases

Table V *Placental findings and Apgar scores (1–5 min)*

Placental findings	No	Apgar Scores ≤7 (no)	(%)
Normal	169	44	6
Macroscopical findings			
Velamentous insertion	1?	6	50
Pl circumvallate	13	5	39
Ablation	9	6	66
Cord prolapse	?	?	100
Microscopical findings			
Embryonal persistence	54	1	22
Ramification defects	51	13	25
Fibrosis	73	15	21
Retardation	41	10	25
Inflammation	49	1?	25

of toxemia but not on a clinically significant scale (1 24)

Table V reveals that only certain gross examination findings were of clinical significance velamentous insertion of the umbilical cord placenta circumvallate cord prolapse and ablation of the placenta

Wigglesworth (24) Fox & Sen (9) and Benirschke & Driscoll (4) obtained similar results The changes revealed at gross examination do not correlate with those in relative placental weight (RPW) (Table II) Bleeding during pregnancy and delivery was seen in connection with both placenta circumvallate and ablation of the placenta The gross examination findings were conclusive in the cases of asphyxia (Table V) Asphyctic infants were observed in over 50% of the cases which is twice the frequency for infants with normal placentas

The RPW analysis (Table II) reveals that embryonal persistence was frequent microscopically in the large placentas According to Table IV these placentas are those of the mothers with diabetes (e g Vogel 25) hepatosis (e g Lauslahti 19) malformed infants (e g Hallman & Kouvalainen 12) specific inflammations (e g Essbach 7) Especially ramification defects and fibrosis were found in small placentas These placentas were encountered in toxemic mothers (e g Frank 10) and in cases of prolonged gestation and premature births (e g Vogel 26)

The RPW clarly seem to give a more accurate picture of the significance of placental weight in maternal diseases and of the infant s postnatal prognosis than the weight of the whole placenta a result which differs from Nummi's (22) finding

As Table V shows asphyxia was involved in 26% of the findings in normal placentas On the other hand the percentage of asphyxia among placentas with maturation defects ranged from 21 to 25 Thus the present histological classification showed no characteristic significance for the infant s asphyxia

The present study suggests that a large placenta and above all rapid circulatory changes in the placenta are the main factors which significantly influence the infant s prognosis The extensive placental infarctions (1) and retroplacental hemorrhage were examples of this The placenta seems to be a particularly adaptable organ able to compensate extensive pathological changes For instance secondary angiomatosis is often noticeable in cases of fibrosis toxemia or prolonged gestation and of ... together with trophoblastic cell proliferation This kind of secondary change is seen in many cases of other placental defects (17)

REFERENCES

1 Aherne W & Dunnill M S Quantitative aspects of placental structure J Path Bact 91 123 1966
2 Aladjem S Perrin E & Fanaroff A Placental score and neonatal outcome Obstet Gynecol 39 ... 1972
3 Benirschke K Examination of the placenta Obst Gynecol 18 309 1961
4 Benirschke K & Driscoll S G The Pathology of the Human Placenta Springer Verlag New York 1967
5 Bradford W D The case for careful examination of the placenta Clin Pediat 12 716 1968
6 Döring W & Kloos K Morphologische Routindiagnostik der Placenta Münch Med Wschr 106 1849 1964
7 Essbach H Pathologische Morphologie der Sekundinae und ihre Beziehungen zu Gedeihstörungen zur verfrühten Gerburt und zum Absterben der Leibesfrucht In Plazenta und Eihäute (ed H Essbach & I Röse) Gustav Fischer Verlag Jena 196.
8 Foss J and Vogel M Über Beziehungen zwischen Implantationschäden der Plazenta und Plazentationsstörungen Z Geburtsh Perinat 176 36 1972
9 Fox H & Sen D K Placenta extrachorialis A clinico-pathological study J Obstet Gynaecol B Commonw 79 32 1972
10 Frank G Histologische Befunde bei Gestose placenten Verh Dtsch Ges Pathol 51 381 1967
11 Fujikura T Significance of single umbilical artery report from collaborative study of cerebral palsy Am J Obstet Gynecol 94 274 1966
12 Hallman N & Kouvalainen K Die grosse Plazenta – ein frühes Zeichen von kongenitalen Krankheiten Praxis 56 119 1967
13 Hellman L M & Hertig A T Pathological changes in the placenta associated with erythroblastosis of the fetus Am J Pathol 14 111 1938
14 Hörmann G Plazenta und lues Ein Beitrag zu Diagnose und Prognose konnatalen Syphilis Arch Gynäk 184 481 1954
15 Hörmann G & Lemtis H Die menschliche Placenta In Klinik der Frauenheilkunde und Geburtshilfe Band 3B (ed H Schwalm & G Döderlein) Urban & Schwartzenberg München 1965
16 Kloos K Vorschlag einer einheiten makro- und mikropathologischen Untersuchungsmethode bei perinatalen Todfällen Pädiat Pädol 3 60 1967
17 Kloos K & Vogel M Pathologie der Perinatalperiode pp 23–25 G Thieme Verlag Stuttgart 1974
18 Kouvalainen K Hjelt L & Hallman N Placenta in the congenital nephrotic syndrome Ann Paediat Fenn 8 181 1962

19 Lauslahti K On intrauterine death Acta Obstet Gynecol Scand *50* 356 1971
20 Lauslahti K Examination of the placenta and the umbilical cord (Finnish) Duodecim *88* 1057 1972
21 Little W A Significance of placental/fetal weight rations Am J Obstet Gynecol *79* 134 1960
22 Nummi S Relative weight of the placenta and perinatal mortality Acta Obstet Gynecol Scand Suppl 17 1972
23 Scott J M & Jordan J M Placental insufficiency and small for-date babies Am J Obstet Gynecol *113* 873 1972
24 Wigglesworth J S Morphological variations in the insufficient placenta J Obstet Gynaecol Br Commonw *71* 871 1964
25 Vogel M Plakopathia diabetica Virchows Arch Path Anat *343* 51 1967
26 Vogel M Epikritische und Prognostische Plazentadiagnostik Munch Med Wschr *110* 1187 1968 1968

Submitted for publication Febr 6 1978

K Lauslahti M D
Department of Pathology
Tampere Central Hospital
SF 33520 Tampere 52
Finland

Acta Obstet Gynecol Scand 58 169–173 1979

MENSTRUAL REGULATION AS A METHOD FOR EARLY TERMINATION OF PREGNANCY

Matti Mandelin and Olavi Karjalainen

From Departments I and II of Obstetrics and Gynecology University Central Hospital Helsinki Finland

Abstract 116 women with documented or suspected pregnancy underwent an endometrial aspiration for early termination Their menses delay was between 7 and 22 days A standard 3 mm Vabra® aspirator was used 90 5% were actually pregnant The success rate was 97 1% The total complication rate was 6 8% the most common complication being endometritis Three patients required a re-evacuation because of prolonged bleeding In this series there were two ectopic pregnancies and nine cases of ovum abortivum of which one later turned out to be a hydatiform mole The procedure was well tolerated by the patients No sick leave was given The postoperative bleeding averaged 10 days in primigravid and 7 days in parous patients

Efforts to avoid the risks associated with legal abortion performed during the second or late first trimester of pregnancy have lead to the application of new techniques such as vaginal administration of prostaglandin derivatives (4) and the use of minisuction curettage in the termination of early pregnancy The latter method also called menstrual regulation was first reported by Karman and Potts in 1972 (7) It has since been widely tested in various countries (1 3 10 14 16) and is now common practice in many centres e g in the U S (8) Menstrual regulation (MR) is performed in most centres up to 14 days after the expected date of menstruation In most studies it has proved to be a safe and effective method for early pregnancy termination (1 3 14 16) but some investigators have reported failure rates exceeding 10% in proven cases of pregnancy (1) The rate of unnecessary aspirations done to nonpregnant women is reported to vary between 5 and 30% depending on the length of the menses delay (1 10) Unnecessary measures are obviously done even in cases of proven pregnancy because an appreciable number of defective ova would be expelled spontaneously during the next weeks of pregnancy (9) As regards the arrangement of postabortal fertility control one has to consider that the first menstrual cycle after a conventional abortion may be ovulatory in only 10 per cent (11) although rates as high as 85% have been reported (2) Knowledge of restoration of ovulatory function after menstrual regulation seems to be lacking

The present study was designed both to evaluate the effectiveness of endometrial aspiration as a means of early abortion and to chart the re establishment of ovulation after this procedure

PATIENTS AND METHODS

The series consisted of 116 normally menstruating women whose menstrual delay was between 7 and 22 days The measures were performed as an out patient procedure by the same physician Before the curettage the patients were informed about the nature of the procedure and given contraceptive advice In cases of frank cervicitis the procedure was postponed a few days while antibacterial treatment was given A great majority of the patients had already been tested for pregnancy by remitting doctors If the test was negative or no previous tests existed a pregnancy tube test (Pregnosticon All In® Organon Company Oss Holland) was performed Other laboratory evaluation consisted of a Papanicolau smear and cultures for trichomonas candida and gonococci for each patient

The curettage was performed by using standard Vabra® curettes with a 3 mm wide metal cannula and a plastic compartment for tissue collection (Ferrosan A/S Copenhagen Denmark) A conventional electric vacuum pump was used a a vacuum source No preoperative medication was employed Parous patients received no local anaesthesia while for most (80%) of the nulliparae a paracervical block was administered The vacuum pressure used in the procedure was 0 5 kp/cm No cervical dilatation was employed All the suction material was sent to a histopathological examination done by the same pathologist The histologic criteria for pregnancy included decidua with villi the occurrence of throphoblasts even without villi or gestational hyperplasia of the endometrium If the patient desired an IUD (Copper T 200 Leiras Turku Finland) was inserted at the end of the procedure The time required for the curettage averaged 5 min

After the procedure the patients were allowed to leave the hospital immediately and resume their usual activities No sick leave was given and the patients commenced

Table I *Age and parity distribution of the patients*

Age	Primigravidae	Parous	Total	%
–18	1		1	1 0
19–25	27	6	33	28 0
26–30	15	22	37	32 0
31–35	7	22	29	25 0
36–	2	14	16	14 0
Total	52	64	116	100 0

their work on the same or the following day An information leaflet about possible complications was given to the patients and they were instructed to measure their basal body temperature and observe their bleeding until the first postoperative check up 3 weeks later A weekly blood sample for plasma progesterone determination was taken from 29 patients Plasma progesterone determinations were carried out using a radioimmune assay method based on the Devilla Janne method without however column separation (5 6) A plasma progesterone level above 5 ng/ml (15 9 nmol/l) was accepted as the criterion for ovulation (12)

RESULTS

Patient characteristics

The age of the patients ranged between 17 and 45 years with approximately two thirds between 19 and 30 years (see Table I) The proportions of primigravidae and parous women were almost equal The length of amenorrhoea and menses delay are illustrated in Table II About 72% of the patients had an amenorrhoea of between 36 and 45 days the menses delay being between 11 and 20 days in 84% of the cases There were very few women with less than 36 or more than 50 days of amenorrhoea

Laboratory examinations

The histopathological findings are given in Table III In the 103 intrauterine pregnancies the product of conception was normal in 87 patients (85%) while in 9 cases (9%) the histopathological diagnosis was a typical ovum abortivum One of these was later found to be a hydatiform mole In both tubal pregnancies the endometrium showed a decidual reaction There were 7 additional cases with the same histological finding Three of these cases were failures while 4 had a normal uneventful postoperative course The finding in these cases suggests an inadequate tissue yield in preparing the histological specimen

There were no false positive pregnancy tests while 12 patients including the two cases of extrauterine pregnancy had a false negative pregnancy test The culture for gonococci was positive in three cases

Acceptability of the procedure

The patients estimates of pain involved in the procedure are shown in Table IV Practically all primigravidae felt some pain in spite of the local anaesthesia whereas almost one fifth of the parous patients felt no pain although no anaesthesia was used

Six patients felt dizzy after the procedure requiring observation at the polyclinic for about half a hour There was no clear correlation between the pain felt and the symptoms

Complications

There were no surgical complications Three patients were re evacuated because of cramps and heavier postoperative bleeding In all these cases the reason was found to be retained tissue One patient required a blood transfusion

There were 3 failures in the series (2 9%) The histopathological diagnosis in all these patients was reactio decidualis In one case the procedure was repeated the other two underwent a standard suction evacuation

There were no severe postoperative infections in the series Four patients including one with a positive gonococcal culture were treated because of endometritis All infections occurred in patients who received an IUD All complications occurred in patients with a proven pregnancy

The duration of postoperative bleeding averaged

Table II *Length of amenorrhoea and menses delay*

Length of amenorrhoea			Menses delay		
Days	No	%	Days	No	%
–35	4	3 5	–10	15	13 0
36–40	22	19 0	11–15	61	52 5
41–45	61	52 5	16–20	36	31 0
46–50	26	22 5	21–	4	3 5
51–	3	2 5			
Total	116	100 0	Total	116	100 0

Table III *Histology of aspirated material and final diagnosis*

	Diagnosis			
Histology	Intra uterine preg nancy	Tubal preg nancy	Not preg nant	Total
Normal pregnancy	87	0	0	87
Ovum abortivum	8	0	0	8
Hydatiform mole	1	0	0	1
Decidual reaction	7	2	0	9
Secretory endometrium	0	0	4	4
Proliferative endometrium	0	0	7	7
Total	103	2	11	116

8 days (range 0–21 days) About 20% of the patients without an IUD felt contractions during the post operative period for some days The two cases of tubal pregnancy reported discomfort from the first postoperative day on and were operated after the onset of more severe symptoms

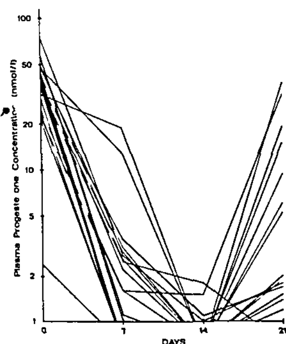


Fig 1 Plasma progesterone concentrations after the procedure (logarithmic scale)

Table IV *Subjective pain ratings immediately after the procedure*

	Primi gravidae	Parous	Total
No pain	1	11	1
Slight	0	26	46
Moderate	31	76	57
Severe	0	1	1
Total	5	64	116

The patient with molar pregnancy had an un eventful postoperative course until 2 months later when she returned to the polyclinic complaining of irregular bleeding and general symptoms of preg nancy Examination then revealed uterine enlarge ment corresponding to a 16 to 18 weeks pregnancy Ultrasound examination was typical of hydatiform mole The patient underwent a prostaglandin induc tion and suction curettage

Restoration of ovulation

Plasma progesterone samples were obtained from 29 patients of whom 24 had been pregnant at the time of the procedure Their plasma progesterone levels are illustrated in Fig 1 By the 21st post operative day only 3 patients had values above 16 nmol/l (5 ng/ml) suggesting ovulation Four addi tional patients showed somewhat less elevated val ues Of all pregnant patients 17% had a rise in BBT suggesting possible ovulation by the 21st postopera tive day This observation fits with the onset of their first menstruation after the menstrual regula tion procedure

Approximately 60% of all pregnant patients had their first menstruation before the 40th postopera tive day The mean procedure–menstruation inter val was 37 days range 21–65 days

DISCUSSION

In this study on 116 women with documented or suspected pregnancy evacuated with a standard Vabra aspirator the success rate was 97% while the total complication rate was 6 8% Similar studies from other centres show a total complica tion rate of between 0 2 and 11 0% (14) being in general of the same order as in standard vacuum extraction techniques used in later first trimester abortion (13 15)

Some 10% of the women applying for MR procedure were not pregnant thus representing the group undergoing an unnecessary operation This percentage is lower than generally reported (10) possibly due to the fact that the majority (70%) of the patients were more than 13 days overdue It is possible that referring doctors were more liable to send patients with positive pregnancy tests The use of more sensitive tests will naturally minimize the possibility of unnecessary procedures

A disadvantage of this method is that the detection of extrauterine pregnancies is rather difficult The histopathologic diagnosis of decidual reaction may as well be due to a failure in the evacuation procedure as to extrauterine pregnancy or as shown in this series to a failure in tissue processing for histology Therefore a histological diagnosis of decidual reaction calls for very close follow up In our opinion menstrual regulation always demands a histopathological examination of the aspirated tissue

A thorough follow up is necessary also in order to reveal possible failures another problem hardly encountered with conventional abortion technique To reduce failure incidence it may be advisable to wait until the patients are at least 14 days overdue as all the failures in this series occurred in patients whose menses delay was shorter than that

Most MR studies have been done using soft Karman plastic cannulas In this study a standard 3 mm Vabra aspirator was used but the rigid and relatively narrow cannula presented no problems There were no perforations and in the few cases where the cannula was blocked by tissue the blockage was easily overcome by increasing the vacuum The Vabra aspirator which has a chamber for tissue collection was found well suited for the purpose Soft plastic cannulas of course reduce the risk of perforation

Boyd & Holmstrom (2) found in their series of conventional abortion that on the basis of endometrial biopsy about 50% of the patients had ovulated by the 22nd postoperative day Although in this study the corresponding figure was only some 13% some immediate postabortal contraception is nevertheless called for

In this series there were 8 proven cases of ovum abortivum and 1 case of hydatiform mole representing an 8 7% incidence of defective ova of the intrauterine pregnancies This incidence was clearly lower than we expected on the basis of reports by investigators involved in human fertility studies (9) Thus the importance of pathologic ova as a cause of unnecessary artificial termination may not be of great significance

CONCLUSION

The menstrual regulation type of pregnancy termination has some clear advantages compared with the standard VE procedure later in the first trimester As a simple rapid measure done in the earliest weeks of pregnancy it reduces the emotional stress that is associated with the termination of an unwanted pregnancy in a later stage It allows the patients to resume their normal activities immediately Its complication rates are within reasonable limits and combined with efficient follow ups it contributes very favourably to the management of unwanted pregnancies

REFERENCES

1 Atienza M F Burkman R T King T M Burnett L S Lau H L Parmley T M & Woodruff J D Menstrual extraction Am J Obstet Gynecol 121 490 1975
2 Boyd E F & Holmstrom E G Ovulation following therapeutic abortion Am J Obstet Gynecol 113 469 1972
3 Brenner W E Edelman D A & Kessel E Menstrual regulation in the United States A preliminary report Fertil Steril 26 289 1975
4 Bygdeman M Borell U Leader A Lundstrom V Martin J N & Eneroth P Induction of first and second trimester abortion by the vaginal administration of 15 methyl $PGF_{2\alpha}$ methyl ester *In* Advances in Prostaglandin and Thromboxane Research (eds B Samuelson & R Paoletti) vol ? p 693 Raven Press New York 1976
5 Devilla G O Jr Roberts K Wiest W G Mikhail G & Flickinger G A specific radioimmunoassay of plasma progesterone J Clin Endocrinol Metab 35 458 1972
6 Janne O Apter D & Vihko R Assay of testosterone progesterone and 17α hydroxyprogesterone in human plasma by radioimmunoassay on hydroxyalkoxypropyl Sephadex J Steroid Biochem 5 155 1974
7 Karman H & Potts M Very early abortion using syringe as vacuum source Lancet I 1051 197?
8 Lancet Editorial p 947 May 1976
9 Leridon H Démographie des échecs de la reproduction *In* Les Accidents Chromosomique de la Reproduction (eds A Boué & C Thibault) p 13 IN SERM Paris 1973
10 Miller E R Fortney J A & Kessel E Early vacuum aspiration Minimizing procedures to nonpregnant women Fam Plan Perspect 8 33 19 6

11 Purola E & Nerdrum T Re establishment of menstruation after abortion Ann Chir Gynaecol Fenn *57* 618 1968
12 Ross G T Cargille C M Lipsett M B Rayfard P L Marshall J R Strott C A & Rodbard D Pituitary and gonadal hormones in women during spontaneous and induced ovulatory cycles Rec Prog Horm Res *26* 1 1970
13 Sigurdsson K Aborter vid Nacka sjukhus 1975—somatiska komplikationer och preventiv teknik Sv Lakartidningen *74* 318 1977
14 Stringer J Anderson M Beard R W Fairweather D V I & Steele S J Very early termination of pregnancy (menstrual extraction) Br Med J *3* 7 1975
15 Tietze C & Murstein M C Abortion Factbook 1975 Reports on Population/Family Planning No 14 2nd ed December
16 Van der Vlugt T & Piotrow P T Menstrual regulation update Population Report Series F No 4 May 1974

Submitted for publication Jan 17 1978

Matti Mandelin
Department of Obstetrics and
Gynecology I and II
University Central Hospital
Helsinki
Finland



Acta Obstet Gynecol Scand 58 175–178 1979

THE TREATMENT OF POSTMENOPAUSAL SYNDROME BY MONTHLY ORAL DOSES OF QUINESTROL

Oscar E Jaschevatzky Shmuel Anderman Amos Shalit
David Kampf and Stephan Grunstein

From the Department of Obstetrics and Gynecology Hillel Jaffe Memorial Government Hospital Hadera Israel

Abstract Seventy patients between the ages of 37 and 59 suffering from the menopausal syndrome were included in a clinical trial and treated for a period of 6 to 18 months Out of the seventy 43 were suffering from spontaneous and 27 from surgical menopause Forty of them were given 1 mg of quinestrol and 30 received placebo The drug was administered orally in a one tablet dose once a month An improvement took place in 35 (87 5%) of the women receiving quinestrol but in only 15 (50%) of those receiving placebo Among the patients with spontaneous menopause an improvement was seen in 22 out of 25 (88%) receiving quinestrol compared with 9 out of 18 (50%) receiving placebo Tolerance of the drug was good and most of the laboratory tests as well as blood pressure and body weight showed statistically non significant changes This kind of treatment is especially suitable when daily intake is undesirable

It has been reported that the use of small daily doses of quinestrol a synthetic estrogen resulted in the remission of postmenopausal symptoms in majority of patients (3 7 9) Quinestrol was synthetized in 1961 and chemically consists of 3 cyclopenthyl ether of ethinyl estradiol One of the prominent features of this estrogen is the prolonged effect obtained when given per os Quinestrol is absorbed through the lymph system stored in fatty tissues and then gradually released (8) In monthly doses of 1 mg it has a moderate trophic effect on the endometrium and a pronounced influence on the vaginal mucosa (1)

Following the studies performed by Sands (7) Zarate & Greenblatt (9) and Hankin (3) Guixa et al (2) reported in 1971 on disappearance of the menopausal syndrome in up to 93% of the patients after 3 months quinestrol intake of 1 mg monthly oral doses

The purpose of this paper is to report the results of a study carried out using quinestrol in 1 mg monthly oral doses in a group of women suffering from the menopausal syndrome

MATERIALS AND METHODS

The clinical material comprised of 70 women aged 37 to 59 years who were suffering from the menopausal syndrome Of these 43 were suffering from spontaneous and 27 from surgical menopause The women were chosen in accordance with the following criteria

1 A complaint of at least the 4 main symptoms of menopause heat flushes sweating nervousness and insomnia

2 Cessation of menstruation of at least one year in spontaneous menopause and at least 3 months post operatively in surgical menopause

3 No treatment with either hormones or tranquilizers during the previous year

Once included in the study every woman underwent both a gynecological and physical examination including blood pressure measurement and weight recording at the beginning of treatment and every 3 months thereafter

Forty women of the considered patients were given quinestrol 1 mg and 30 received placebo Of the 40 women receiving quinestrol 25 had a spontaneous menopause and 15 were surgically induced Of the 30 patients treated by placebo 18 were in the spontaneous and 12 in the surgical menopausal group The drug was administered orally in a one tablet dose once a month for 3 months after which period it was given once every 4–6 weeks in accordance with the request of the patient The duration of the treatment ranged from 6 to 18 months None of the 70 women knew whether they received quinestrol or placebo Both tablets were similar in appearance Follow up of all patients was done by the same physicians

The results were graded as follows complete improvement when all complaints had disappeared partial improvement when there was only a relief in the symptoms and failure when there was no improvement of symptoms whatsoever

In 10 patients blood samples were taken prior to the onset of treatment and 6 months following it in order to determine calcium phosphorus lipids cholesterol proteins glucose by standard methods and triglycerides by a colorimetric procedure normal ranges 30–200 mg% (Oxford Laboratories reagents were used) In 2 women serum FSH and LH were measured by RIA in order to determine the estrogenic effect of quinestrol on the hypothalamic pituitary axis Samples were taken before onset and 1 3 24 48 72 hours and 1 2 3 and 4 weeks after initiation of treatment

Table I *Clinical evaluation of patients*

Group	Improvement				Failure		Dropped out	
	Complete		Partial					
	No	%	No	%	No	%	No	%
Quinestrol (40)	19	47 5	16	40	2	5	3	7 5
Placebo (30)	3	10	12	40	15	50	0	–

Table II *Clinical response of menopausal patients taking Quinestrol*

Type of medication	Spontaneous menopause								Surgical menopause							
	Improvement				Failure		Dropped out		Improvement				Failure		Dropped out	
	Complete		Partial						Complete		Partial					
	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
Quinestrol	12	48 0	10	40 0	–	–	3	12 0	7	46 7	6	40 0	2	13 3	–	
Placebo	3	16 7	6	33 3	9	50 0	–	–	–	–	6	50 0	6	50 0	–	

RESULTS

[Eva]luation of the results obtained in the group as a whole [show]ed that an improvement had taken place in 35 [(8]7 5%) of the women receiving quinestrol but only in 15 (50%) of those receiving placebo (Table I) In the group of women with spontaneous menopause an improvement was seen in 22 (88%) out of 25 of those treated with quinestrol and in 9 (50%) out of 18 of those treated with placebo In the group with surgical menopause there was an improvement in 13 (86 7%) out of 15 receiving quinestrol and in 6 (50%) of the 12 patients receiving placebo There was no significant difference in the relief of symptoms between the 2 groups with either spontaneous or surgical menopause concerning the effectiveness of quinestrol Partial improvements and failures of treatment are given in Table II

The observed side effects were skin rash in 2 patients thrombophlebitis in 1 patient vaginal bleeding in 3 patients and nausea in 4 patients

Skin rash was observed for 1 or 2 days immediately after taking the medication Although no special treatment was needed the quinestrol was suspended after 3 and 4 months of intake respectively The patient with thrombophlebitis had had in the past 3 similar episodes which were not reported initially by the patient before being included in the study The current episode appeared after 6 months of quinestrol treatment it was superficial in nature required bed rest and the medication was discontinued Vaginal bleeding appeared in 3 patients after 4 6 and 16 months of treatment All patients underwent diagnostic curettage which showed a proliferative endometrium therefore the treatment was continued

Laboratory tests as well as blood pressure and body weight showed statistically non significant changes Triglycerides however showed a rise of 19 9% from the mean of pretreatment levels to those present after 6 months of treatment (Table III) However the comparison of the triglycerides levels before and after treatment using the Wilcoxon test reveals non significant difference ($p>0\ 10$)

Baseline serum FSH and LH in the 2 patients in whom they were measured were found to be in the postmenopausal range before treatment Although a significant decline in FSH and LH levels was obtained 2 to 3 hours after the quinestrol intake the maximum suppression was seen 7 days following the initiation of treatment Thereafter the curve remained steady throughout the following 3 weeks (Figs 1 and 2)

Table III *Laboratory studies performed before and after 6 months of treatment*

Examination	Before		After		P value (by Wilcoxon test)
	Mean	*±S E*	*Mean*	*±S E*	
Total proteins	7 11	0 15	7 30	0 09	ns
Albumin	4 66	0 13	4 93	0 05	ns
Globulins	2 45	0 14	2 36	0 07	ns
Calcium	9 60	0 11	9 57	0 71	ns
Phosphorus	3 68	0 15	3 40	0 13	ns
Glucose	72 66	2 72	69 00	3 93	ns
Cholesterol	233 33	14 92	244 40	8 13	ns
Total lipids	843 41	78 00	843 50	37 10	ns
Triglycerides	196 11	33 10	235 22	3 77	ns

ns = non significant

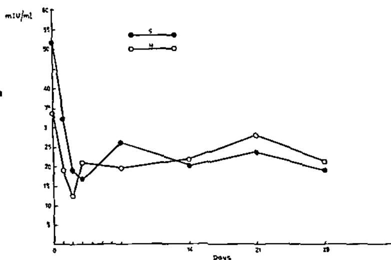
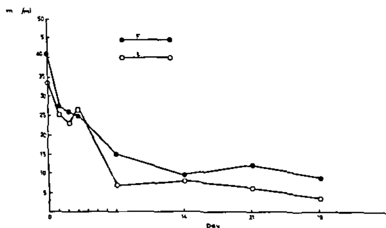


Fig 1



Figs 1 and 2 FSH and LH serum levels before onset and during quinestrol therapy

F 2

DISCUSSION

For a long time the menopausal syndrome was considered a clinical manifestation of the rise of gonadotropins which occurs in women during menopause (4) This hypothesis is no longer accepted It has been proved that the syndrome is due to a neuro-hormonal imbalance and that it develops following the loss of ovarian estrogen production The rise of gonadotropins is due to the lack of negative feedback of estrogens on the pituitary (6) Therefore when non hormonal therapy gives no response the most rational approach to treatment of the syndrome lies in the administration of estrogens

Our experience in treating the menopausal syndrome using monthly doses of quinestrol has proved of similar benefit to that obtained using daily estrogens An additional conclusion to be drawn from our study is that the efficacy of treatment was identical in cases of spontaneous and surgical menopause

Tolerance to treatment was generally good The most frequent side effect—nausea—was slight transient and in no case lasted more than twenty four hours

In the 3 cases in which bleeding appeared no pathological proliferation of endometrium was found in the curettings This fact indicated that these were probably cases of withdrawal bleeding

The rise observed in the triglycerides mean level

was also reported using other estrogens (5) However the statistical comparison of the triglycerides levels before and after treatment using the Wilcoxon test did not show a significant change therefore it is difficult to establish the precise significance of the increase in the mean level

In our opinion the method is specially suitable in surgical menopause provided substitutive therapy is indicated This prevents the necessity of a daily intake during long periods

In conclusion treatment of the menopausal syndrome with monthly or periodical doses of quinestrol is an acceptable method to be used especially in cases in which daily intake is undesirable

ACKNOWLEDGEMENTS

This research was supported by a grant from Laboratorio Elea" (Buenos Aires Argentine) which supplied also the trial preparations We would like to express our gratitude to the mentioned institution for its help and generosity

REFERENCES

1 Bagnati E P Zapata A C & Guelfi M N El quinestrol en el tratamiento del climaterio Pren Med Argent 59 155 1972
2 Guixa H L Cronenberg F M Faccone J G & de la Parra I Nuevo enfoque terapéutico del climaterio comunicación previa Pren Med Argent 57 2079 1971
3 Hankin H Quinestrol therapy in the menopausal patient Int J Fert 12 2 9 1967
4 Kopera H Treatment of the climateric Organorama 12 3 1975
5 Lauritzen Ch The female climateric syndrome significance problems treatment Acta Obstet Gynecol Scand Suppl 51 49 1976
6 Lauritzen Ch Selected aspects of endocrinology and epidemiology of the climateric Acta Obstet Gynecol Scand Suppl 65 11 1977
7 Sands R X Quinestrol and the menopausal syndrome Int J Fertil 12 235 1967
8 Williams K I H Layne D S Hobkirk R Nilsen M & Blahey P R Metabolism of doubly labeled ethinyl estradiol 3-cyclopentyl ether in woman Steroids 9 275 1967
9 Zarate A & Greenblatt R B Quinestrol in the menopause Int J Fertil 12 233 1967

Submitted for publication March 28 1978

Oscar E Jaschevatzky
Dept of Obstetrics and Gynecology
Hillel Jaffe Memorial Government Hospital
Hadera
Israel

Acta Obstet Gynecol Scand 58 179–181 1979

SERUM LEVELS OF TOTAL DEHYDROEPIANDROSTERONE AND TOTAL ESTRONE IN POSTMENOPAUSAL WOMEN WITH SPECIAL REGARD TO CARCINOMA OF THE UTERINE CORPUS

Kjell Carlstrom [1] Mats Goran Damber [3] Mirjam Furuhjelm [1]
Ingemar Joelsson [3] Nils Olov Lunell[2] and Bo von Schoultz[3]

From the Departments of Obstetrics and Gynaecology of Sabbatsberg Hospital Stockholm [2]Huddinge Hospital Huddinge the [3]Department of Gynecologic Radiology Radiumhemmet Stockholm and [4]Umea University Hospital Umea Sweden

Abstract Serum levels of total dehydroepiandrosterone and total estrone were determined in 18 postmenopausal women with carcinoma of the uterine corpus (stage I grade 1–3) and in 40 healthy postmenopausal women Elevated levels of both steroids were found in the carcinoma group for dehydroepiandrosterone 2010±195 vs 1?99±117 nM $p<0\ 01$ and for estrone 2 38±0 ?4 vs 1 36±0 11 nM $p<0\ 001$ Dehydroepiandrosterone as well as the precursors of estrone are almost exclusively of adrenal origin in the postmenopausal woman Thus these findings indicate a role of the adrenal cortex in the etiology of corpus carcinoma either by providing increased levels of substrate for the peripheral synthesis of estrone or a direct action of adrenal androgens on the endometrial tissue

The role of estrogens in the etiology of corpus carcinoma is frequently discussed and controversial Some investigators have found elevated levels in blood and increased urinary excretion of estrone in postmenopausal women with endometrial cancer (2 4 22) Others have reported no increases in these respects (11) Estrone is formed in the postmenopausal woman almost exclusively by peripheral conversion of 4 androstone 3 17-dione (15) This key precursor is of predominantly adrenal origin in these individuals (16) Increased levels of 4-androstene 3 17-dione may therefore reflect an increased activity of the adrenal cortex An association between adrenal hyperplasia and carcinoma of the endometrium has also been reported in autopsy materials (18) Increased levels of estrone can therefore be attributed to an augmented utilization of the available precursor or to increased synthesis of this i e of 4 androstene 3 17-dione An increased conversion of 4-androstene 3 17 dione to estrone in postmenopausal women with endometrial carcinoma has been reported (9) which in turn might have a relationship to the high incidence of obesity in this group of patients (18 20 27)

As one part of a study concerning the role of adrenocortical activity in gynecological cancer this communication deals with the concentrations in the peripheral blood of total (free + conjugated) dehydroepiandrosterone (to more than 95% dehydroepiandrosterone sulphate) and total estrone (to more than 85% estrone sulphate) in postmenopausal women with special regard to carcinoma of the uterine corpus

MATERIALS AND METHODS

Eighteen postmenopausal women aged 6?–88 years (mean 74 1±1 7 years) with a histologically confirmed endometrial carcinoma were included in the study All patients had a stage I tumor Three of these were histologically grade 1 eleven were grade 2 and four grade 3 tumors

The control material consisted of 40 postmenopausal women without any known disease aged 60–85 years (mean 72 1±1 1 years) No hormonal preparations or other medications known to interfere with the hormone assays were used in the two groups Venous blood samples were drawn in the morning and the sera were stored at −?0 until use In the carcinoma patients the samples were collected before treatment

Serum levels of total dehydroepiandrosterone were measured by a modification of the procedure of Metcalf (19) Briefly the method includes dilution of the serum sample 1 10000 with 0 04 M sodium acetate buffer pH 4 5 heating at 1?0 for 75 min extraction with diethyl ether and radioimmunoassay using anti-dehydro-epiandrosterone 17-carboxymethyloxime bovine serum albumin (Hypolab S A Coinsins Switzerland) The recovery of [7 ^{3}H]dehydroepiandrosterone sulphate added prior to hydrolysis was 87 1±1 5% (n=?7) The variation between duplicates expressed as S D for 40 duplicate pairs in the range 1270–47 0 nM (mean ?640 nM) was ?15 nM (8 1%) Analysis of a single serum sample in 16 different assays gave a mean concentration value of

Table I *Peripheral serum levels of total estrone and dehydroepiandrosterone in healthy postmenopausal women and in postmenopausal women with corpus carcinoma*

	n	Age (years)	Serum total estrone (nM)	Serum total dehydroepiandrosterone (nM)
Healthy women	40	72 1±1 1	1 36±0 11	1299±117
Patients with endometrial carcinoma	18	74 1±1 7	2 38±0 24	2010±195

4170 nM with a S D of 500 nM (12 1%) The least concentration to differ significantly from the reagent blank (difference 2 S D) was 444 nM

Serum concentrations of total estrone were determined by radioimmunoassay after enzymatic hydrolysis with purified Helix pomatia enzyme and ether extraction (6) The antibody used was anti-estrone 6-thyroglobulin (Batch TH 1 Miles Yeda Ltd Rehovot Israel)

Values are given as mean ± S E M statistical calculations were performed using Student s t test and assuming al distribution of the individual values

RESULTS AND COMMENTS

Serum levels of total estrone and of total dehydroepiandrosterone were significantly higher ($p<0.001$ and $p<0.01$ in the group of women with endometrial carcinoma than in the control group (Table 1) Estrone sulphate is by far the most abundant blood estrogen in non pregnant humans (5 10 17) The values of total estrone (more than 85% estrone sulphate) are of the same magnitude as the sum of total estrone + estradiol 17β reported by Aleem and co-workers (2) The elevated estrone concentration found in the patients with corpus carcinoma are in accordance with most previous investigations in this field (2 4 22)

Data are scarce regarding the serum levels of adrenal C_{19} steroids notably 4 androstene 3 17 dione and dehydroepiandrosterone in patients with corpus carcinoma Dehydroepiandrosterone occurs almost entirely in its sulphoconjugated form and is almost exclusively of adrenal origin (21) Dehydroepiandrosterone sulphate is quantitatively the most important steroid in human peripheral circulation and its serum concentration does indeed reflect the activity of the adrenal cortex (3 7 12 13 21 26)

The serum levels of total dehydroepiandrosterone (almost entirely dehydroepiandrosterone sulphate in the control group are in accordance with previously published figures (1 7 26) The increased levels found in the patient with corpus carcinoma were not unexpected considering the increased frequency of adrenal hyperplasia reported for this category (18) Since the elevated levels of dehydroepiandrosterone indicate an increased activity of the adrenal C_{19} steroid production it can be assumed that the other principal adrenal C_{19} steroid i e 4 androstene 3 17-dione will show elevated levels too (16) This would in turn contribute to the increased levels of estrone in women with endometrial carcinoma

The discussion in the literature about endometrial cancer and its connection with endogenous steroid production has been confined almost entirely to the estrogens However the main endocrinological disorders associated with endometrial carcinoma are adrenal hyperplasia and the polycystic ovary syndrome (18) It should be recalled that these conditions are chiefly characterized by an excessive production of androgens often leading to virilization It is known from studies in rats that androgens can stimulate uterine growth and that androgen receptors are found in the uterine cytosol (8 14 20) Furthermore it has been reported that androgens are capable of translocating the uterine estrogen receptor into the cell nucleus (24 25) Without depreciating the role of estrogens in the etiology of corpus carcinoma the results given above indicate an important role of androgens in this chain of events

REFERENCES

1 Abraham G E & Macroulis G B Effect of exogenous estrogen on serum pregnenolone cortisol and androgens in postmenopausal women Obstet Gynecol 45 271 1975

2 Aleem F A Mamdouh A M Hin Cheung Hung & Romney S L Plasma estrogen in patients with endometrial hyperplasia and carcinoma Cancer 38 2101 1976

3 Baulieau E E Corpechot C Dray F Emiliozzi R Lebeau M C Mauvais Jarvis P & Robel P An adrenal secreted "androgen" Dehydroepiandrosterone sulfate Its metabolism and tentative generalization of the metabolism of other steroid conjugates in man Rec Progr Hormone Res 21 411 1965

4 Benjamin F & Deutsch S Plasma levels of fractionated estrogens and pituitary hormones in endometrial carcinoma Am J Obstet Gynecol *126* 638 1976

5 Brown J B & Smyth B J Oestrone sulphate—the major circulating oestrogen in the normal menstrual cycle? J Reprod Fertil *24* 142 1971

6 Carlstrom K & Sköldefors H Determination of total oestrone in peripheral serum from non pregnant humans J Steroid Biochem *8* 1127 1977

7 Cattaneo S Forti G Fiorelli G Barbieri U & Serio M A rapid radioimmunoassay for determination of dehydroepiandrosterone sulphate in human plasma Clin Endocr *4* 505 1975

8 Giannopoulus G Binding of testosterone to cytoplasmic components of the immature rat uterus Biochem Biophys Res Commun *44* 943 1971

9 Hausknecht R U & Gusberg S B Estrogen metabolism in patients at high risk for endometrial carcinoma Am J Obstet Gynecol *116* 981 1973

10 Hawkins R A & Oakey R E Estimation of oestrone sulphate oestradiol 17β and oestrone in peripheral plasma Concentrations during the menstrual cycle and in men J Endocrinol *60* 3 1974

11 Judd H L Lucas W E & Yen S S C Serum estradiol 17β and estrone levels in postmenopausal women with and without endometrial cancer J Clin Endocrinol Metab *43* 272 1976

12 Judd H L McPherson R A Rakoff J S & Yen S S C Correlation of the effects of dexamethasone administration on urinary 17 ketosteroid and serum androgen levels in patients with hirsutism Am J Obstet Gynecol *128* 408 1977

13 Korth Schutz S Levine L S & New M I Dehydroepiandrosterone sulfate (DS) levels a rapid test for abnormal adrenal androgen secretion J Clin Endocrinol Metab *42* 1005 1976

14 Lerner L J Hilf R Turkheimer A R Michel I & Engel S L Effects of hormone antagonists on morphological and biochemical changes induced by hormonal steroids in the immature rat uterus Endocrinology *78* 111 1966

15 Longcope C Metabolic clearance and blood production rates of estrogens in postmenopausal women Am J Obstet Gynecol *111* 778 1971

16 Longcope C Steroid production in pre and post menopausal women *In* The Menopausal Syndrome (ed R B Greenblatt V B Mahesh and P G Donough) p 6 Medcom Press New York 1974

17 Loriaux D L Ruder H J & Lipsett M B The measurement of estrone sulfate in plasma Steroids *18* 463 1971

18 Lucas W E Causal relationships between endocrine metabolic variables in patients with endometrial carcinoma Obstet Gynecol Survey *29* 507 1974

19 Metcalf M G Dehydroepiandrosterone sulfate in plasma Hydrolysis extraction and radioimmunoassay Steroids *28* 311 1976

20 Rizkallah T H Tovell H M M & Kelly W G Production of estrone and fractional conversion of circulating androstendione to estrone in women with endometrial carcinoma J Clin Endocrinol Metab *40* 1045 1975

21 Roberts K D & Lieberman S The biochemistry of the 3β hydroxy Δ^5 steroid sulfates *In* Chemical and Biological Aspects of Steroid Conjugation (ed S Bernstein and S Solomon) p 219 Springer Verlag Berlin Heidelberg and New York 1970

22 Rome M Brown J B Mason T Smith M A Laverty C & Fortune D Oestrogen excretion and ovarian pathology in postmenopausal women with atypical hyperplasia adenocarcinoma and mixed adenosquamous carcinoma of the endometrium Brit J Obstet Gynecol *84* 88 1977

23 Rochefort H & Lignon F Differences between the estradiol and testosterone receptors in rat uterus Eur J Biochem *48* 503 1974

24 Rochefort H & Garcia M Androgen on the estrogen receptor I Binding and in vivo nuclear translocation Steroids *28* 549 1976

25 Ruh T S Wassilak S G & Ruh M F Androgen induced nuclear accumulation of the estrogen receptor Steroids *25* 257 1975

26 Sekihara H Ohsawa N & Ibayashi H A radioimmunoassay for serum dehydroepiandrosterone sulfate Steroids *20* 813 1972

27 Siiteri P K & McDonald P C Role of extraglandular estrogen in human endocrinology *In* Handbook of Physiology Section 7 Endocrinology vol II 1 (ed R O Greep and E B Ashwood) p 615 Am Physiol Soc Washington D C 1973

Submitted for publication Jan 17 1978

Kjell Carlstrom
Hormone Laboratory
Department of Obstetrics and Gynecology
Sabbatsberg Hospital
S 11382 Stockholm
Sweden

Acta Obstet Gynecol Scand 58 183–186 1979

PROPHYLACTIC SALPINGO OOPHORECTOMY IN CANCER OF THE CERVIX

Katarina Bremme and Nina Einhorn

From the Department of Gynecologic Oncology Radiumhemmet Karolinska sjukhuset Stockholm

Abstract It is considered that the presence of infection during the course of treatment for cancer of the cervix can have a bearing of the prognosis (3 5 6 7 9 14 22) In a number of series the survival rate has been lower for such patients suffering from pelvic infection than it has for those without such infection That agressive treatment of infection during the therapy can greatly improve the survival rate was observed by Heyman (9) and Kottmeier (14) Irrespective of the stage reached in the treatment of the cervical cancer Kottmeier recommended immediate salpingo-oophorectomy in patients with acute salpingitis (15) He reported that this measure improved the 5 year survival rate for these patients from 14 to 66% (15) He also reported 5 year survival rates of 21 and 56% for patients with and without infection respectively (14)

It has been debated whether in view of the supposed hormonal dependence of cervical cancer (8 19) the improvement of the survival rate for patients undergoing elective salpingo-oophorectomy might be due to the hormonal consequences of removing the ovaries (15) Arising out of these discussions an investigation was undertaken in 1958 of the effect of prophylactic salpingo-oophorectomy This operation was performed in all patients less than 60 years of age with cancer of the cervix starting in 1959 It was carried out prior to their admission to the Department of Gynaecological Radiotherapy (15) *The measure was discontinued in 1961 because an in*crease was observed in the incidence of intestinal complications

Since the introduction of antibiotic therapy the incidence of severe pelvic infections has diminished Still it was considered that an analysis of this logically designed series might throw light on infection prophylaxis and possibly also on a hormonal influence in carcinoma of the cervix

The prognosis for cancer of the cervix is held to be poorer in younger women (2 4 10 18 21) and the explanation may lie in the hormonal activity of the ovaries If this is the case the survival rate would presumably be higher for patients undergoing oophorectomy than in a control group where the ovaries had not been removed It was also considered that an analysis of the case material might show whether and to what extent the incidence of radiation reactions is influenced by the fact that surgery has been performed prior to radiotherapy

CASE SERIES

The case series comprised 293 patients of up to 60 years of age with histologically verified carcinoma of the cervix who had been admitted to Radiumhemmet for treatment between January 1959 and February 1961 All had previously undergone salpingo-oophorectomy at various gynaecological departments in the Radiumhemmet catchment area The radiotherapy treatment was given with the individualized Stockholm technique which consists of two intracavitary treatments at an interval of 3 weeks followed by conventional external irradiation of the parametrial structures The patients were followed up at Radiumhemmet every 2–3 months during the first year and subsequently at long r intervals The clinical checks were discontinued after 10 years after which the patients were followed by mail and through the parish registration offices None of the patients dropped out of the follow ups

The control group comprised patients with cervical cancer referred to Radiumhemmet in the years 1958 and 1962 These patients were matched with those in the operation group with respect to age and stage of carcinoma with a ratio of 2 controls to each patient in the investigated group (Table I)

RESULTS

The 5 year rates for the operation and control groups are given in Table II with a distribution by stage

The 5 year survival rates for the operation group with the control rates in parentheses were as follows Stage I 85 (86) % stage II A 72 (73) % stage II B 52 (52) % stage III 32 (24) % and stage IV 9 (8) % The 5 year cure rates for the operation and control groups were 62 and 61 % respectively (Table II)

The 5 year survival rate for the patients in the operation group who were less than 50 years of age was 62 % and for those aged 50 years and above 61 % The corresponding figures for the control group were 62 and 59 % (Table III)

Table I *The operation and control groups of patients distributed by age—less than 50 years and 50 years and above*

	Number of patients	
	Younger group <50 y	Older group ≥50 y
Operation group	192	101
Control group	384	202

There was no appreciable numerical or statistically significant difference between the operation and the control groups

Radiation reactions

It has been suggested that pre therapeutic surgical operations have some implications for the development of radiation injuries (1 16 20)

For example the presence of post surgical adhesions might increase the risk of radiation injuries to the small bowel (11 12 13)

The present series provided an opportunity for comparing radiation reaction in on the one hand patients undergoing surgery prior to radiotherapy and on the other the patients comprising the control series who received only radiotherapy

The radiation reaction was graded and examined as described by Kottmeier (16 17)

Bladder injuries

The incidence of bladder injuries in the operation and control groups is given in Table IV with a distribution by grade

The operation group contained 19 patients (6 5%) with mild subjective symptoms (grade I) 5 patients (1 7%) with necrosis of the bladder and haematuria (grade II) and 4 patients (1 4%) with vesico-vaginal fistula (grade III)

The control group contained 13 patients (2 2%) with grade I 23 patients (3 9%) with grade II and 2 patients (0 3%) with grade III injury (Table IV)

Bowel complications

Bowel complications were divided into rectum and sigmoideum injuries and small intestine injuries The incidence of bowel complications in the operation and control groups is given in Table V with distribution by grade

The operation group contained 31 patients (10 6%) with mild bowel symptoms (grade I) 8 patients (2 7%) with painful stools and passage of mucus and blood (grade II) 5 patients (1 7%) with stenosis of the rectum and colostomy (grade III) and 4 patients (1 4%) with fistula of the rectum and sigmoideum (grade IV) Seven patients (2 4%) had stenosis of the small intestine requiring surgical intervention and small bowel resection and in 3 patients (1 0%) there was a perforation of the small bowel requiring surgical intervention Altogether 3 4% of the operated group presented severe small bowel complications (Table V)

The control group contained 17 patients (2 9%) with grade I radiation reaction involving the bowel 45 patients (7 7%) with grade II reaction 11 patients (1 9%) with stenosis of the rectum and sigmoideum requiring colostomy (grade III) and 8 patients (1 4%) with rectal or sigmoideal fistula (grade IV) In 4 patients (0 7%) there was stenosis of the small bowel requiring bowel resection and in 1 patient (0 2%) there was perforation of the small bowel Altogether 0 9% of the control group had severe small bowel complication (Table V)

As may be seen in Table V the incidence of

Table II *The 5 year cure for operation and control series distributed by clinical stage*

Clinical stage	Operation patients			Control series		
	No of patients	5 year cure		No of patients	5 year cure	
		No	%		No	%
I	67	57	85	134	115	86
II A	98	71	72	196	142	72
II B	75	39	52	150	78	52
III	40	13	32	80	19	24
IV	13	1	9	26	2	8
Total	293	181	62	586	356	61

Table III

	Five year cure rate %		
	<50 y	≥50 y	Whole series
Operation group	62	61	62
Control group	62	59	61

small bowel injuries was greater in the operation than in the control group probably owing to the fact that surgery prior to radiotherapy can lead to the formation of adhesions between the small bowel and the pelvic organs The operation group of 293 patients contained 10 patients (3 4%) with stenosis or perforation of the small bowel against 5 out of 586 (0 9%) in the control group The incidences of severe bladder reactions in the operation and the control groups were 1 4 and 0 3% respectively The corresponding figures for rectal and sigmoideum injury comprising grades III and IV were 3 1 and 3 3% (Table V)

DISCUSSION

The 5 year survival rates for the operation and the control groups did not differ appreciably (Table II) Nor was there any difference for the younger sub groups (below 50 years of age) or between the younger and older patients within the operation and control groups (Table III)

Thanks to the benefits of antibiotics and intensive postoperative care infection during the treatment for cancer of the cervix no longer constitutes the menace that it did three or four decades ago and prophylactic salpingo-oophorectomy hardly features in modern therapeutic programmes Confirmation of this fortunate state of affairs is provided by the results of the analysis of the present series

Table IV

Bladder injury		Operation group No	%	Control group No	%
Grade I	Mild subjective symptoms	19	6 5	13	2 2
Grade II	Bladder necrosis and haematuria	5	1 7	23	3 9
Grade III	Vesico-vaginal fistula	4	1 4	2	0 3

Table V

Bowel complications		Operation group No	%	Control group No	%
Grade I	Mild symptoms and signs	31	10 6	17	2 9
Grade II	Painful sores passage of mucus	8	2 7	45	7 7
Grade III	Stenosis of rectum requiring colostomy	5	1 7	11	1 9
Grade IV	Fistula of rectum sigmoideum	4	1 4	8	1 4
	Stenosis of small intestine requiring surgery and small resection	7	2 4	4	0 7
	Perforation of small bowel requiring surgery	3	1 0	1	0 2

As mentioned above the series was discontinued because of an increase in the incidence of complications Confirmation of the increased frequency of radiation complications in the cervical cancer patients undergoing salpingo-oophorectomy prior to radiotherapy is provided by the analysis of the operation series and the comparison with the control group The increase in the frequency of complications involving the small bowel would appear to be accounted for largely by the development of adhesions following surgery prior to radiotherapy

The reported difference in survival rates for younger and older women with cervical carcinoma (2 4 10 18 21) is not evident in any of the comparisons made in this study Furthermore castration prior to the treatment for cervical carcinoma does not seem to affect the prognosis for these patients

REFERENCES

1 Aldridge A H Intestinal injuries resulting from irradiation treatment of uterine carcinoma Am J Obstet Gynecol 44 833 1942
2 Dodds J R & Latour J P A Relationship of age to survival rate in carcinoma of the cervix Am J Obstet Gynecol 82 33 1961
3 Garcia M Rurther observations on tissue dosage in cancer of the cervix uteri Am J Roentgenol 73 35 1955
4 Gauwerky F Neue Gesichtspunkte zur Frage der Abhangigkeit der Heilbarkeit von Uteruskarzinomen vom Lebensalter Strahlentherapi 96 345 1955
5 Goldscheider G Prognostic significance of rise in temperature in course of radium treatment of cancer of cervix J Obstet Gynaecol Br Emp 50 20 1943

6 Graham J B Sotto L S J & Palouchek F P Carcinoma of the Cervix Saunders Philadelphia 1962
7 Henriksen E Pyometra associated with malignant lesions of the cervix and the uterus Am J Obstet Gynecol 72 884 1956
8 Hertz R Cromer J K Young J P & Westfall B B Observations on the effect of progesterone on carcinoma of the cervix J Nat Cancer Inst 11 867 1951
9 Heyman J The resk of infection in gynecological radiotherapy Hygiea 459 and 497 1926
10 Jentys W Rustowski J Uterine cervix cancer in young women Gin Pol XLIII 3 353 1952
11 Joelsson I Radiotherapy of carcinoma of the uterine cervix with special regard to external irradiation Act Radiol Suppl 302 1970
12 Joelsson I Raf L & Soderberg G Stenosis of the small bowel as a complication in radiation therapy of carcinoma of the uterine cervix Acta Radiol Ther Phys Biol 10 593 1971
13 Joelsson I & Raf L Late injuries of the small intestine following radiotherapy for uterine carcinoma Acta Chir Scand 139 194 1973
14 Kottmeier H L Carcinoma of the Female Genitalia pp 80 and 147 Williams & Wilkins Co Baltimore 1953
15 Kottmeier H L Förhandlingar vid Nordisk För enings Obst och Gyn Kongress i Stockholm 1958
16 Kottmeier H L Complications following radia therapy in carcinoma of the cervix and their trea ment Am J Obstet Gynecol 88 854 1964
17 Kottmeier H L & Gray M J Rectal and bladder injuries in relation to radiation dosage in carcinoma of the cervix Am J Obstet Gynecol 82 74 1961
18 Lindell A Carcinoma of the uterine cervix In dence and influence of age Act Radiol Suppl 9 1952
19 Nathanson I T & Kelley R N Medical progress hormonal treatment of cancer N Engl J Med 245 1 & 180 1952
20 Powel Smith C Factors influencing the incidence of radiation injury in cancer of the cervix J Can Assoc Radiol 14 137 1965
21 Tarlowska L Hlimak I Medvey W & Skowr sky S Results of treatment of invasive cancer of the cervix uteri Am J Obstet Gynecol 105 869 1969
22 Whelton J A Significance of infection in carcinoma of the cervix Obstet Gynecol 26 441 1965

Submitted for publication Jan 25 1978

Katarina Bremme
Department of Gynecological Oncology
Radiumhemmet
Karolinska Hospital
S 10401 Stockholm
Sweden

Acta Obstet Gynecol Scand 58 187–189 1979

TREATMENT OF VULVAL EPITHELIAL LESIONS BY PULSED HIGH FREQUENCY THERAPY

M Gronroos P Liukko L Rauramo and R Punnonen

From the Department of Obstetrics and Gynaecology University Central Hospital Turku Finland

Abstract The effect of pulsed high frequency therapy has been investigated in 25 patients who had various chronic vulval lesions resulting in continuous annoying pruritus smarting or pain resistant to conventional therapy The beneficial effect of pulsed high frequency therapy was either definite or good in 80% of all the cases

Continuous annoying vulval pruritus smarting or pain resistant to therapy is a common syndrome in several lesions of the vulval epithelium especially chronic vulvitis and lichen sclerosus et atrophicus (Kraurosis vulvae) It is known that changes in the terminal vascular system and nutritional disturbances play a significant role in their etiology Whether this is due to functional disturbances of the vegetative nervous system or to some other reasons for instance hormonal causes is not known for certain Corresponding symptoms can be provoked moreover by dysplasia pre invasive carcinomas such as Morbus Bowen and Morbus Paget and already invasive vulval carcinomas The symptoms may be encountered in the vulval region also after treatment of the last mentioned diseases

The literature contains numerous reports on a great variety of treatments of which the commonest are various cortisone and estrogen ointments vitamin ointments local anesthetics and alcohol injections In addition if the symptoms have been very strong vulvectomy has been used even in the treatment of benign diseases Ultrashort wave diathermy has yielded good results in certain cases As far as we know pulsed high frequency therapy (curapulse) has not been used before in the treatment of vulval diseases It was in fact by serendipidy that we observed the beneficial effect of this therapy on vulval symptoms when we treated the lumbosacral syndrome of a patient by curapulse the symptoms from the vulval region of this patient with Bowen s disease disappeared concurrently We therefore decided to investigate the effect of the therapy on a larger material

Character of and indications for therapy

The curapulse device can be used to give both ultrashort wave diathermy and athermic pulsed high frequency therapy The biological effects of the latter may be regarded as the same as those of ultrashort wave diathermy with the difference that no continuous elevation of temperature ensues (3) A high frequency current of 27 12 MHz (wave length 11 062 m) and a pulse time of 400 microseconds are the technical characteristics in curapulse treatment The pulse frequency can be varied over the range 15–200 Hz

Pulsed high frequency therapy has been administered especially when there are foreign bodies (metal vascular prosthesis IUCD) in the patient The same applies if there is an acute infection recent trauma hemorrhagic tendency or defective arterial circulation or when there is on the patient s skin a plaster cast sutures a fistula or moisture of various types and also if the patient complains that the heat (ultrashort wave therapy) causes side effects or aggravation of the condition

MATERIAL AND MODE OF TREATMENT

The material consisted of 25 patients treated at the Department of Obstetrics and Gynaecology University Central Hospital Turku in 1975–1977 who suffered from vulvar pruritus smarting or pain Table I shows that patients with Kraurosis vulvae constituted the largest group These patients had received various courses of treatment before attending the hospital and had then undergone diagnostic procedures e g colposcopy phosphorus scanning (1 2) and biopsy at the out patient department Moreover five patients had previously undergone vul

Table I *Cases with vulval lesion treated with curapulse at the Department of Obstetrics and Gynaecol gy Turku University in 1975–77*

Diagnosis	Symptomless	Better	Unchanged	Total
Kraurosis	7 (58%)	3 (25%)	2 (17%)	12
Chronic vulvitis	1	2	1	4
Vulval pruritus	3	2	–	5
Treated Mb Bowen Mb Paget and vulval carcinoma	1	1	2	4
Total	12 (48%)	8 (32%)	5 (20%)	25

vectomy Other diseases included chronic vulvitis and sequelae (condition after primary therapy) of intraepithelial and invasive vulval carcinomas In five cases no specific histologic diagnosis was verified Pulsed high frequency therapy in sequences of 10–15 single treatments at intervals of a couple of days was administered with the curapulse device A pulse repetition frequency of 62 Hz with 300 W was used The patients were examined before the curapulse therapy two weeks post therapeutically and thereafter at 3–6 month intervals at the Gynecological Cancer Outpatient Department

RESULTS

results are presented in Table I The outcome be regarded as good for the 10/12 patients with kraurosis vulvae seven patients became asymptomatic with both the subjective complaints and the clinical status of the vulval epithelium improving Improvement occurred i e subjective symptoms diminished or the vulval epithelium healed moderately in three patients and in only two patients was there no change The effect was good also in the cases of vulval pruritus of unknown etiology Three of five patients were completely free of symptoms and those of two patients were distinctly relieved The results were poorer both in chronic vulvitis and in the last group which consisted of operated precancerous or cancerous cases The symptoms of both patients with treated carcinoma were unchanged However the patient with treated Bowen s disease has been asymptomatic for two years and it has not been necessary to undertake a new surgical intervention

The results have not changed essentially in the course of the first two follow up examinations As the follow up is still in hand it is not yet possible to estimate accurately the permanence of the therapeutic result But symptoms definitely recurred in some of the patients approximately six months after the termination of therapy

DISCUSSION

Pulsed high frequency therapy produces no permanent elevation of temperature similar to that seen in ultrashort wave diathermy In other words the cooling mechanism—especially blood flow—has time between the impulses to cool the tissue and the patient does not feel the rise in temperature This therapy has been used in e g the following conditions cervical syndrome lumbago arthrosis deformans acute arthritis fresh hematoma acute bursitis prostatitis etc (4 5) The beneficial effect of therapy was either definite or very good in 70% of those and 80% of our cases Contraindications for therapy were stated to be malignant tumours cardiac pacemaker pyrexia active tuberculosis and possibly pregnancy

We have experimented with certain chronic vulval conditions in which troublesome pruritus smarting or pain disable the patient as a new area of indication for curapulse therapy It is a recognised fact that the symptoms are often rather resistant to therapy in spite of the broad selection of treatments We found the effect of pulsed high frequency therapy to be good especially in patients with Kraurosis vulvae and in cases of pruritus of unknown etiology in almost all of which at least remission of symptoms was achieved The treatment is easy to administer places little strain on the patient and is easy to repeat The treatment had to be repeated in some of patients after ½–1 year As the conditions in question especially in the presence of more troublesome subjective symptoms are potentially premalignant or treated malignant their specific follow up is very important The interval before repetition of the treatment and the therapeutic effect after it require further study The effect of therapy e g on wound healing is in our opinion also worth investigating

REFERENCES

1 Gronroos M Lindgren I Laakso L Vilhonen E ^{32}P uptake in vulval dysplastic and malignant epithelium Ann Chir Gynecol Fenn *58* 118 1969
Punnonen R Gronroos M & Lindgren I The value of ^{32}P in the diagnosis of various vulvar lesions Gynecol Oncol *5* 187 1977
3 van Stralen C & van Zutphen H Pulsed high frequency therapy Fysiotherapy The Netherlands *3* 1973
4 Valtonen E J Syvalampohoitokojeitten viimeaikaisesta kehityksesta Laakintavoimistelija No *1* 1 1973
5 Valtonen E J Havaintoja sykelammon (curapuls) kaytosta fysikaalisessa hoidossa Laak voim —fysiotherapeuten *21* 11 1975

Submitted for publication Jan 17 1978

Matti Grönroos
Department of Obstetrics and Gynecology
University Central Hospital
205?0 Turku 5.
Finland

ANNOUNCEMENT

INTERNATIONAL FEDERATION OF GYNECOLOGY AND OBSTETRICS

Secretariat 27 Sussex Place London NW1 England

List of National and International Congresses 1979

Date	Place	Name	Office
1979			
June 6-10	Venice	International Symposium on Fetal Medicine	Prof B Salvadori Dept of OB/GYN University of Parma Parma Italy
June 27 30	Montreux	Congress of the Swiss Society of Gynaecology	Dr H Stamm Geb gyn Abteilung Stadtischen Krankenhaus CH 5400 Baden Switzerland
June 27 30	Amsterdam	International Symposium Medicated IUD s & Polymeric Delivery Systems	Miss K Spanjard Box 20 5340 Oss Holland
October 4 6	Rome	First International Congress on Hormones and Cancer	American Express Company S A I Conversiones Service Italy Piazza di Spagna 32 00187 Rome Italy
October 25 31	Tokyo	IXth World Congress of Gynecology & Obstetrics	Congress Secretariat c/o Simul International Inc 1 8 10 Akasaka Minato-ku Tokyo 107 Japan

Acta Obstet Gynecol Scand 58 191 – 195 1979

AMNIOTIC FLUID PHOSPHOLIPID CONCENTRATIONS IN PREGNANCIES WITH PRE ECLAMPSIA AND/OR INTRAUTERINE GROWTH RETARDATION OF THE FETUS

Julie Skjæraasen

From the Department of Obstetrics and Gynecology Rikshospitalet University of Oslo Oslo Norway

Abstract Amniotic fluid lecithin/sphingomyelin (L/S) ratios were examined in 74 samples from 65 patients with preeclampsia The median values were comparable to those obtained in a reference series up to 36 weeks of gestation whereas the median values after 37 weeks of gestation were found to be significantly smaller in the preeclamptic group ($p<0\ 01$)

According to the present results a L/S ratio ≥2 would in fact guarantee no development of respiratory distress syndrome (RDS) in the infants of preeclamptic mothers On the contrary L/S ratios ≤1 6 may be of limited predictive value in these women since only ⅙ of the children developed RDS When preeclampsia was combined with intrauterine growth retardation of the fetus RDS was found to be less apt to develop

In 21 samples of amniotic fluid from 13 women with idiopathic intrauterine growth retardation of the fetus the L/S ratios were significantly below those in the reference series ($p<0\ 05$) No case of RDS was observed

The synthesis of phospholipid in the fetal lung is influenced by various maternal and fetal factors (3 5 7 8 11 15) Previous studies (16 17) have shown that rhesus immunization and maternal diabetes have an impact upon the maturation of the surfactant system It might be suggested that also in cases of preeclampsia and/or intrauterine growth retardation of the fetus (IUGR) metabolic or circulatory factors may exist which in some way influence the lecithin synthesis in the alveolar cells

The aim of the present study was

1 to examine the lecithin/sphingomyelin (L/S) ratios in pregnancies with preeclampsia and/or IUGR
2 to correlate the results to the clinical outcome concerning respiratory distress syndrome (RDS)
3 to evaluate the reliability of the L/S ratio in predicting RDS following these pregnancy complications

In order to obtain a more comprehensive study of the incidence of RDS after these pathological pregnancies a retrospective investigation of case records was undertaken

MATERIAL AND METHODS

L/S ratio study Amniotic fluid was obtained from patients treated in the Department of Obstetrics and Gynecology Rikshospitalet during the five year period 1973-1977 The samples were collected by transabdominal amniocentesis by transuterine puncture at cesarean sections or by puncture of the amniotic sac during delivery Amniotic fluid grossly contaminated with blood or meconium was discarded

The number of patients and amniotic fluid samples in the different groups and subgroups are listed in Table I Mild preeclampsia means women with blood pressure ranging between 140/90 and 160/110 mm Hg measured at least twice with intervals and <2 0/00 protein in urine (Esbach s test used for quantitative protein measurements) Severe preeclampsia means women with blood pressure >160/110 mm Hg and/or >2 0/00 protein in urine As shown in Table I 22 of the infants in the preeclampsia group had birth weights at or below the 2 5 percentile according to Bjerkedal *et al* (1) 64 per cent and 13 per cent in the severe and in the mild preeclampsia subgroup respectively

Idiopathic IUGR was defined as a neonate with a birth weight ≤2 5 percentile without any known malformation or genetic disorder and no preeclampsia in the mother

The L/S ratios obtained in patients with preeclampsia and/or IUGR were compared to those measured in a reference series of 120 pregnancies (174 samples) in which the surfactant synthesis was assumed to be normal These were rhesus immunized women with a rhesus negative baby in the actual pregnancy and/or no pathological hemolysis (Liley zone I) and women with normal pregnancies

The L/S ratio in the last sample collected before the delivery was correlated to the clinical outcome as for RDS Seventy four of these samples were taken in connection with the delivery and the remaining four within one week before delivery These results were compared to clinical outcome observed in another series of predelivery L/S ratios where cases of pre-eclampsia IUGR and diabetes had been excluded

The determinations of the L/S ratios were performed by a modified Gluck s method as previously described (16) In four samples with low L/S ratios the concentration of palmitic acid was measured by gas liquid chromatography according to the method described by Lindback (17)

Total estrogens in urine were examined by the method described by Oakey (13)

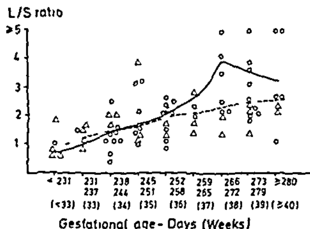


Fig 1 L/S ratios in 74 samples of amniotic fluid from 65 women with preeclampsia and/or IUGR (≤2 5 weight per centile) related to gestational age
△ samples from cases with preeclampsia and IUGR
○ samples from cases with preeclampsia and no IUGR
— median values in the reference series --- median values in the preeclampsia group

Retrospective study of case records The incidence of neonates with RDS following preeclampsia and/or IUGR was calculated on the basis of the records of infants born in the Department of Obstetrics and Gynecology Rikshospitalet 1970-1976 *This incidence was compared to the incidence of* S observed among infants of gestational age <266 days ered in the department 1973 1976 Children of diabetic hers were excluded

Gestational age has in the text been given in terms which refers to completed weeks (i e 39 weeks = 273 279 days) The criteria for RDS has been the same as those used in the previous publications (10)
The Wilcoxon two-sample test was used for statistical analysis The significances given are for two-sided tests

RESULTS

Fig 1 shows the L/S ratios in the samples from the preeclamptic group As may be observed there was a wide range in the results obtained The *L/S ra* showed no relationship to the severity of the pre lampsia There were some L/S ratios that were h for the period of gestation at 33 36 weeks The me an values were found to be similar to those obta in the reference series up to 36 weeks At gestation age ≥37 weeks *however the median values tend* to be lower than in the reference series especially those with IUGR When combining the data from weeks of gestation to term the difference between L/S ratios in the preeclamptic group and in the refe ence series was found to be significant (p<0 01)

The *L/S* ratios measured in the idiopathic IUG group (Fig 2) were generally found to be lower th in the reference series and by combining the da from 34 weeks to 40 weeks a statistically signific difference was obtained (p<0 05)

The groups under study showed characteris differences with respect to the frequency of RDS the preeclamptic group one child of an eclam mother died during delivery and the results from remaining 64 children are presented in Fig 3 R did not develop among the neonates with a predel ery L/S ratio >1 6 or among those born after a g tional age of ≥37 weeks Twenty five children w born before 37 weeks of gestation and had L/S ra ≤1 6 Nine of them developed RDS of whom RDS occurred in three cases (L/S ratios 1 5 1 6 1 6) whereas in the remaining six cases (L/S ra <1 5) RDS *was relatively severe and three needed* pirator ventilation for several days All infants s vived It ought to be noticed that in these 25 ba mentioned only two of ten with IUGR and as ma seven of the 15 without IUGR suffered from RD Sixteen infants born at gestational ages <36 we *had no RDS despite predelivery L/S ratios <1 6*

The palmitic acid concentration was measure

Table 1 *The different groups of patients included in the present study*

Disorder	Patients N	Amniotic fluid samples N	Neonates with birthweights ≤ 2 5 percentile N	%
Preeclampsia/Eclampsia				
Mild preeclampsia	38	43	5	13
Severe preeclampsia	25	29	16	64
Eclampsia	2	2	1	
Total	65	74	22	
Idiopathic intrauterine growth retardation	13	21	13	

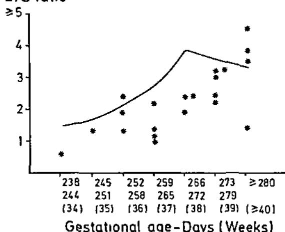


Fig 2 L/S ratio in 21 samples of amniotic fluid from 13 womeen with IUGR related to gestational age
★ samples from cases with IUGR — median values in the reference series

four samples with L/S ratios 0 8 1 1 1 1 and 1 2 and found to be 0 021 0 064 0 064 and 0 027 mmol/l respectively RDS occurred in those infants with palmitic acid concentrations 0 021 and 0 027 mmol/l

Among the 13 infants with idiopathic IUGR there was no case of RDS despite very low L/S ratios in the predelivery samples collected by cesarean section in three patients (L/S ratios 0 6 1 1 and 1 4)

In the majority of the pregnancies showing IUGR the urinary excretion of total estrogens were below 2 S D of mean normal values Otherwise no correlation was found between the urinary total estrogens excretion and the L/S ratio or the development or RDS in the neonate

The results obtained in the retrospective study of case records are presented in Table II It has to be emphasized that few of the women having premature deliveries had prolonged rupture of the membranes since such patients most often received corticosteroid treatment and hence had to be excluded from the study As shown in the table the incidence of RDS was lower in the preeclamptic group than among infants of mothers with premature deliveries during the intervals 28 33 and 36-37 weeks of gestation but approximately the same for both groups at 34 35 weeks of gestation

The percentage of infants delivered by cesarean section was considerably higher in the preeclamptic group ranging from 18 80 per cent and 3 11 per cent in the preeclamptic and the premature group respectively Among the children with idopathic IUGR only one developed RDS This infant with a birthweight of 1 000 g was born at a gestational age of 32 weeks and had an Apgar 1 minute score of 3

DISCUSSION

Gluck and his colleagues have reported that preeclampsia and hypertension in the mother may accelerate the fetal pulmonary maturity by two to six weeks and measurements of the amniotic fluid L/S ratios have lent support to this statement (7 8) Nayes *et al* (14) have claimed that fetal stress which causes adrenal hyperplasia also may induce lecithin synthesis in the fetal lung at an earlier gestational age than normal Freeman *et al* (5) have attempted to evaluate the fetal stress by measurements of estriol excretion and performance of an oxytocin challenge test Their data did not support the contention that fetal pulmonary

Table II *The frequency of RDS in cases of preeclampsia and idiopathic intrauterine growth retardation as compared to that observed in a group of infants born before 266 days of gestation (cases of preeclampsia IUGR and diabetes exluded)*
n = No of infants with RDS N = Total no of infants CS % = Percentage of infants delivered by caesarean section

Gestational age Days	Preeclampsia			Idiopathic IUGR		Reference group of prematurity		
	n/N	% RDS	CS %	n/N	CS %	n/N	% RDS	CS %
< 196						10/10	100	0
196 237	3/10	30	80	1/1	0	36/74	49	5
238 251	8/25	32	60	0/5	80	20/63	32	11
252 265	4/56	7	18	0/10	50	9/95	10	3
≥ 66	1/369	0 3	10	0/68	20			

Ret ospect e record st dy from the Departme t of Obstetrics and Gynecology Rikshosp talet 1970 1976 (See te t)

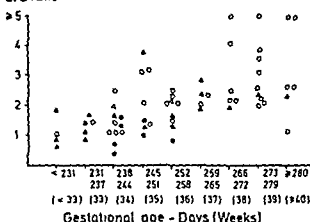


Fig 3 The correlation between L/S ratios and subsequent development of RDS in infants of preeclamptic mothers
) samples *from* cases *with preeclampsia and IUGR*
) samples from cases with preeclampsia and no IUGR
Filled symbols infants who developed RDS

maturity as evaluated by the L/S ratio is commonly advanced in the stressed pregnancies *Doran et al* (3) found among women with hypertensive disorders L/S ratios slightly below normal mean values from 34 weeks of gestation to term

Since an amniocentesis entails a certain risk to the fetus it has only been performed before the 37th week when it has been considered necessary to induce labor because of *maternal disease or the presence of signs* of fetus at risk Accordingly then the amniotic fluid samples collected in the present investigation *prior* to the 37th week of gestation referred to a higher number of pregnancies with severe pathological disturbances as compared to those collected after the 37th week of gestation This obviously raises questions about the comparability of the L/S ratios recorded among the women under study although no correlation between the severity of the maternal disease and *the L/S ratio could be observed*

Some exceptionally high L/S ratios for the gestational age exceeding the range in the reference series *may of course indicate accelerated maturation in these* cases Generally however the L/S ratios obtained in the preeclamptic group did not signal an acceleration of the pulmonary maturity but showed on the contrary a significantly delayed surfactant synthesis after 37 weeks of gestation (Fig 1)

From the present study it must be concluded that the occurrence of RDS in neonates of preeclamptic mothers is strongly linked to prematurity (Fig 3 and Table II) But even in highly premature infants of preeclamptic mothers the risk of RDS seems to be negligible provided the L/S ratio is mature thus indicating a high reliability for the test On the other hand a low L/S ratio (<1 6) which is usually considered to signal a substantial risk of RDS (Fig 4) was found to be of limited predictive value in cases of preeclampsia since only ⅓ of the infants developed RDS Measurements of palmitic acid concentrations might presumably give a more reliable information *concerning the RDS risk All four cases studied* showed palmitic acid concentrations below the critical value of 0 073 mmol/l (Lindback 1976) those two who *contracted RDS had considerably lower values*

When the preeclampsia is combined with IUGR there seems to be a decreased tendency to development of RDS As shown in Fig 3 only two among the ten premature infants with L/S ratios ≤1 6 delivered in such pregnancies suffered from RDS as compared to seven among 15 infants with no IUGR

In the retrospective study of case records (Table II) the frequency of RDS among neonates of preeclamptic mothers was not found to be much different from *that observed among* ' normal premature babies If a delivery by cesarean section involves an increased risk of RDS (4 6 20) the data obtained might indicate *that premature infants of pre eclamptic mothers* have a decreased tendency to develop RDS as compared to normal premature infants

In cases of idiopathic IUGR there is significant delay in surfactant synthesis (Fig 2) As mentioned animal studies (2) and clinical studies (14) have indicated an association between fetal adrenal hyperplasia and accelerated maturation of pulmonary surfactant synthesis It is possible that low L/S ratios in cases of idiopathic IUGR might be associated with

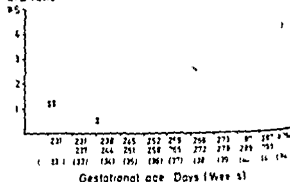


Fig 4 The correlation between L/S ratios and subsequent development of RDS in a reference series (see text)
infant with no RDS ■ infant with RDS

hypoplasia of the adrenal glands The data obtained in the idiopathic IUGR group in the L/S ratio study as well as in the study of case records give support to the view held that these infants are most unlikely to develop RDS (19) A low L/S ratio in cases of idiopathic IUGR did not appear to indicate an enhanced risk of RDS and the test was found to be of very limited predictive value in this connection

In a previous publication (*16*) we reported that neonates of diabetic mothers may develop RDS despite the presence of ample lecithin concentrations In the present study the reversed phenomenon seems to exist namely no development of RDS in spite of an *insufficient surfactant production This indicates* clearly that a lack in the lecithin synthesis cannot represent the only factor responsible for this kind of respiratory disturbancies Attention should therefore be drawn on other possible factors such as variations in the blood volume in the extracellular fluid and in the pulmonary circulation It might also be that other phospholipids present in the surfactant layer in the lung alveoli may have an impact upon the functional maturity of the fetal lung (9 18) The possible influence of other phospholipids than lecithin will be further investigated

ACKNOWLEDGEMENTS

The author is indepted to Professor K Bjøro Department of Obstetrics and Gynecology for his kind support of the study The author also wants to thank the colleagues in the Department for valuable assistance

REFERENCES

1 Bjerkedal T Bakketeig L & Lehmann E H Percentiles of birth weights of single live births at different gestation periods Acta Pædiatr Scand *62* 449 1975

2 DeLemos R A Shermeta D W Knelson J H Kotas R & Avery M E Acceleration of appearance of pulmonary surfactant in the fetal lamb by administration of corticosteroids Am Rev Respir Dis *102* 459 1970

3 Doran T A Malone R M Benzie R J Jones Owen V Thompson D W & New M L Amniotic fluid tests for fetal maturity in normal and abnormal pregnancies Am J Obstet Gynecol *125* 586 1976

4 Farrell P M & Avery M E Hyaline membrane disease Am Rev Respir Dis *111* 657 1975

5 Freeman R K Bateman B G Goebelsmann U Arce J J & James J Clinical experience with the amniotic fluid lecithin/sphingomeylin ratio II The L/S ratio in stressed pregnancies Am J Obstet Gynecol *119* 239 1974

6 Gabert H A Bryson M J & Stenchever M A The effect of cesarean section on respiratory distress in the presence of mature lecithin/sphingomyelin ratio Am J Obstet Gynecol *116* 366 1973

7 Gluck L Kulovich M & Gould J B The effect of maternal disease on maturation of human fetal lung Pediatr Res *6* 409 1972

8 Gluck L & Kulovich M Lecithin/sphingomyelin ratios in amniotic fluid in normal and abnormal pregnancy Am J Obstet Gynecol *115* 539 1973

9 Hallman M Kulovich M Kirkpatrick E Sugarman R G & Gluck L Phosphatidylinositol and phosphatidylglycerol in amniotic fluid Indices of lung maturity Am J Obstet Gynecol *125 613 1976*

10 Lindback T Frantz T Skjæraasen J & Graven S Phospholipids in amniotic fluid Acta Obstet Gynecol Scand *53* 219 1974

11 Lindback T Amniotic fluid lecithin concentrations in pregnancies complicated by hypertensive disorders and intrauterine growth retardation Acta Obstet Gynecol Scand *55* 355 1976

12 Lindback T Amniotic fluid palmitic acid concentration and prediction of fetal lung maturity Scand J Clin Lab Invest *36* 659 1976

13 Oakey R E Bradshaw L R A Eccles S Stitch S R & Heys R F The rapid estimation of oestrogens in pregnancy to monitor foetal risk Clin Chim Acta *15* 35 1967

14 Naeye R L Harcke H T Jr & Blanc W A Adrenal gland structure and the development of hyaline membrane disease Pediatrics *47* 650 1971

15 Nelson G H Amniotic fluid phospholipid patterns in normal and abnormal pregnancies Am J Obstet Gynecol Scand *105* 1072 1969

16 Skjæraasen J & Lindback T Influence of intrauterine haemolysis on the amniotic fluid phospholipid concentration Acta Obstet Gynecol Scand *54* 319 1975

17 Skjæraasen J & Lindback T Phospholipid concentrations in amniotic fluid from diabetic pregnant women Acta Obstet Gynecol Scand *55* 225 1976

18 Skjæraasen J & Stray Pedersen S Phosphatidylinositol and phosphatidylglycerol in amniotic fluid in normal and diabetic women *In* Abstract 6th Nordic Congress in Perinatal Medicine Oulu Sept 1977

19 Usher R H Clinical and therapeutic aspects of fetal malnutrition Pediatr Clin North Am *17* 169 1970

20 Usher R H Allen A C & McLean F H Risk of respiratory distress syndrome related to gestational age route of delivery and maternal diabetes Am J Obstet Gynecol *111* 826 1971

Submitted for publication April 27 1978

Julie Skjæraasen
Department of Obstetrics and Gynecology
Rikshospitalet
Oslo 5
Norway

ANNOUNCEMENT

IXth World Congress of Gynecology and Obstetrics is to be held October 25 31 1979 in Tokyo Japan

Official languages English French Spanish and Japanese

Scientific Program

- Special lectures
  - *Reproductive endocrinology* by Prof Kenneth J Ryan Harvard Medical School U S A
  - *Comparative aspects of fetal differentiation* by Prof Alfred Jost College de France France
  - *Recent progress in gynecologic oncology* by Prof Per Kolstad Norwegian Radium Hospital Norway
- Plenary sessions
  - *Social aspects of obstetrics and gynecology including contraception*
  - *The climacteric and postmenopause including hormone therapy*
  - *Endocrinology of the menstrual cycle*
  - *Physiopathology of intrauterine fetal growth*
  - *Reproductive immunology*
  - *The role of obstetric management in reducing fetal mortality and morbidity*
  - *Premalignant lesions of the female genital tract*

In addition there are *Correlated Seminars Seminars* and *Free Communications* covering wide range of topics of current interest

Social Program and *Program for Accompanying Persons*

Deadlines

Early registration July 31 1979

Application Free communication papers films and scientific exhibits February 28 1979

Those who are interested in attending the Congress are invited to write to

Secretariat
IX World Congress of Gynecology and Obstetrics
c/o Simul International Inc
Kowa Bldg No 9
1 8 10 Akasaka Minato-ku
Tokyo 107 Japan

Xth World Congress on Fertility and Sterility The Inter-tional Federation of Fertility Societies will sponsor the X World Congress to be hosted by the Spanish Fertility Society at the National Palace of Expositions and Congresses Madrid Spain September 20-26 1980

There will be two days for Pre-Congress Symposia and Post Graduate Courses followed by a program on the following themes

- Spermatogenesis
- Ovulation
- Psychosexual and social aspects of fertility
- Problems of gamete transportation
- Immunology in reproduction
  Controle of fertility
- Neuroendocrinology of reproduction
- Fertilization and implantation
- Environmental and iatrogenic aspects of reproduction
- Genetics in reproduction

Please reply to
A Campos da Paz
Chairman Scientific program
Av Copacabana 664 AP 606
Rio de Janeiro Brazil

International Symposium on *Clinical Importance of Surfactant Defects* will be held in Hamburg October 31 November 2 1979

Information

Professor Dr P v Wichert
I Medizinische Universitätsklinik
Hamburg Eppendorf
Martinistrasse 52
D 2000 Hamburg 20
Germany

Acta Obstet Gynecol Scand 58 197–201 1979

FETAL BREATHING MOVEMENTS AND MATERNAL EXERCISE

Karel Marsal Olof Löfgren and Gerhard Gennser

From the Department of Obstetrics and Gynecology Allmänna Sjukhuset University of Lund Malmo Sweden

Abstract Earlier statements that fetal breathing movements (FBM) are sensitive to changes in the fetal homeostasis prompted the study of the effect of maternal exercise on FBM and fetal heart rate Forty women in the last trimester of gestation were subjected to a work load (80 W) for 5 min on a bed ergometer cycle in 30 of them FBM were recorded by A mode ultrasound and in 10 the fetal heart rate was monitored by continuous ultrasound Maternal blood pressure pulse rate blood pH and pCO and transcutaneous pO_2 were also followed The FBM showed a transient marked increase in incidence immediately after the end of the exercise No changes in basal level or in baseline variability of the fetal heart rate were found in the recovery period after work Some possible causes of the observed FBM alterations are discussed The findings imply that after this particular form of stress FBM are a more sensitive indicator of the physiological state of the fetus than the fetal heart rate

Our knowledge of whether maternal physical activity affects the human fetus in normal gestation is at present incomplete Only few clinically normal pregnant women subjected to exercise tests have shown any changes in the fetal heart rate (14 16 24 26 27) It has been suggested that measurements of fetal breathing movements (FBM) in man provide a more sensitive indication of fetal physiological state than does fetal heart rate (FHR) (5) This concept has been supported by some observations on animals (19 23) but was recently doubted in a study on sheep (29) The present investigation in uncomplicated human pregnancy studies the effect of a defined maternal work load on the FBM compared with that on the FHR

MATERIAL AND METHODS

Two groups of pregnant women participated in the study after giving their informed consent All had singleton pregnancies with the fetal head in pelvic inlet

Group I The effect of maternal exercise on FBM was examined in 30 women in the 30th–42nd (median 35th) gestational week The pregnancy was normal in all respects in 27 women two had mild cholestasis of pregnancy and one showed ABO isoimmunization The maternal age ranged from 19–38 (median 25 5) years 19 of the women were nulliparae Two women were subsequently delivered by elective cesarean section (indications elderly primigravida longstanding sterility) the rest by the vaginal route Four were delivered by a low vacuum extraction two because of acute fetal distress the other two because of a prolonged second stage of labor

Group II In the second group of ten pregnant women FHR was monitored in relation to maternal exercise as for technical reasons FHR could not be continuously measured in Group I at the same time as the FBM The maternal ages ranged from 18–30 (median 25) years and the gestational ages from 32–37 (median 34) weeks eight of the women were nulliparae All ten women had an uneventful pregnancy and all were delivered vaginally at term Low vacuum extraction had to be used at two deliveries because of acute fetal distress

All the women of both groups gave birth to clinically healthy infants All the infants had Apgar score ≥7 One was born before the end of the 36th week of pregnancy all infants were appropriate for the gestational age according to the Swedish standards for singletons (28) One woman was delivered one day after the investigation all the others had an interval greater than two days to delivery All the women except one tolerated the work test without distress The only exception was a woman with a normal pregnancy who was not included in the study group because measurement could not be carried out She responded with painful hypertonic uterine contractions and extreme tachycardia This response lasted for 10 minutes she subsequently delivered a healthy infant

The investigation was performed during the morning with the women in a semi recumbent position The work load equivalent to 80 W was achieved by exercise on a bed type bicycle ergometer Calibration of the cycle ergometer was controlled by measuring the oxygen uptake at steady state in two male volunteers when pedalling on three different occasions (mean oxygen uptake 1 420 ml/min) The women were exposed to the work load for 5 min after a 30-minute control period Recording continued for another 30 min after the exercise ended

FBM were monitored in Group I continuously by a modified A mode echoscope (Ekoline 20 Smith Kline) as originally described by Boddy and Robinson (2) The records were evaluated according to the method given by Parmelee *et al* (22) The entire record was divided into 20-second periods and the FBM for each period were classified in one of four patterns regular irregular periodic and apneic The

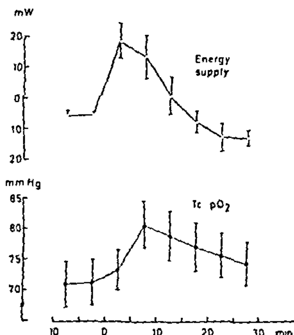


Fig 1 Maternal transcutaneous pO_2 (Tc pO_2) and the relative energy supply to the Tc pO_2 electrode during the exercise test (14 of the women in Group I Means ± SEM for 5 minute periods) The shaded area depicts the exercise period (0-5 min) The energy supply values for each woman are related to the zero point at the start of the exercise

percentage of time for which each of the FBM patterns was present was calculated for every 5 minute period All records were analysed by one of the authors (K M) Maternal breathing was monitored by a thermistor applied to one nostril for identifica ion of any artifacts in the FBM records caused by transmitted maternal respiratory movements

The echoscope used for the FBM measurements could not simultaneously record the FHR Therefore the FHR in Group I was counted visually on the echoscope screen every second minute In Group II the instantaneous FHR was followed continuously before and after the exercise by an ultrasonic Doppler cardiometer (Fetasonde 2100 Roche) (Accuracy of the cardiotachometer is reported by the manufacturer to be ±2 5 per cent of full scale) The FHR traces were analysed manually for mean basal rate and baseline variability for every 5 minute period During the exercise the measurements of FBM and FHR could not be carried out as maternal movements dislocated the ultrasonic transducers being attached to the ma ernal abdomen

Maternal brachial blood pressure was measured every fifth minute The results are presented as the mean arterial pressure calculated according to the formula (8)

mean arterial pressure = ⅓ (systolic + 2 (diastolic pressure))

Maternal heart rate was monitored continuously via conventional ECG chest electrodes

In 20 consecutive tests in Group I maternal capillary blood was sampled on three occasions 10 min before the load immediately after and 15 min after the end of the load The capillary blood was arterialized by dipping the finger tips for 30 sec in a warm water bath Maternal pO_2 and pCO in capillary blood were estimated by conventional electrodes (Instrumentation Laboratory Inc Boston Ma USA)

The maternal transcutaneous pO (Tc pO) was measured in 14 women of Group I by a Radiometer TCM 1 ... T pO_2 (mm Hg) and energy supply to the electrode (mW) necessary to keep a constant temperature (44 5 C) were continuously recorded The Tc pO electrode was Clark type modified according to Huch (13) With this device the correlation between arterial pO_2 and Tc pO in adults measured at the electrode temperature of 44 5 C (within ± 0 1 C) was found to be highly significant (r = 0 9?) The mean difference between arterial pO_2 and Tc pO was 1? mm Hg (SD ± 11 9) (Löfgren 1977 to be published) The electrode was attached to the skin in the subclavicular area with a double adhesive tape After a stabilization time of about 15 min the recording was begun The records were evaluated manually the mean of Tc pO_2 values and of relative levels in energy supply were calculated for every 5-minute period

Statistical evaluation was made by Student s t-test based on intra individual differencies and by correlation analysis

RESULTS

Group I The pregnant women responded to the work load with a significant rise in heart rate The maternal tachycardia was maximum during the exercise and persisted for the next 25 minutes There was also an elevation in maternal mean arterial pressure but this persisted only during the work (Table I)

The maternal Tc pO was stable in the control period it rose during the exercise to reach the maximum level in the first 5 min after the end of the exercise (p < 0 001) (Fig 1) Thereafter Tc pO_2 declined slowly and reached the control level 30 min after the exercise

Table I *Maternal heart rate (beats per min) and maternal mean arterial pressure (mm Hg) during the exercise test (Group I exercise period 0 5 min n = 30)*

Parameter	Min from start −30 0	0 5	6 10	11 15
A Maternal heart rate				
beats/min mean	88	131	95	9?
± SEM	± 0 7	± 4 3	± ?9	± 2?
Sign of diff t		10 ?28	4 456	4 ??
p		< 0 001	< 0 001	< 0 0??
B Mat art pressure				
mm Hg mean	87	106	91	8?
± SEM	± 0 7	± 1 7	± 1 8	± 1 6
Sign of diff t		11 164	1 871	-0 ??
p		< 0 001	n s	n s

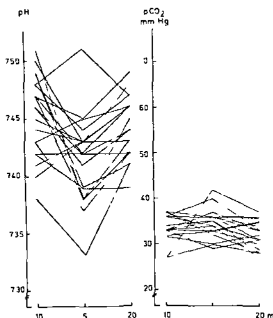


Fig 2 Values of pH and pCO_2 in maternal capillary blood before and after the exercise test in 19 of the women in Group I (Exercise period 0 5 min)

cise The corresponding energy supply to the Tc pO_2 electrode increased to a maximum during the maternal exercise ($p < 0\ 001$) and returned to the control level 10 min later (Fig 1)

Mean pH of the arterialized capillary blood in the control period was 7 45 ± 0 01 (± SEM) (Fig 2) Immediately after the exercise pH had fallen significantly ($p < 0\ 001$) to 7 41 ± 0 01 and returned 15 min later to the control level (7 44 ± 0 01) The mean capillary pCO_2 in the control period was 33 5 ± 0 6 mm Hg A slight non significant increase occurred at the end of the maternal exercise (34 6 ± 0 7 mm Hg) 15 min later the pCO_2 level had decreased to 32 1 ± 0 7 mm Hg (Fig 2)

The pattern of FBM was marked altered by the work test The exercise period was immediately followed by a profound reduction of the relative incidence of apnea ($p < 0\ 001$) and of periodic breathing ($p < 0\ 001$) and by an increase in the incidence of irregular breathing ($p < 0\ 001$) compared with that of the control period The alteration of the fetal breathing patterns subsided gradually and had disappeared 15 min after the exercise (Fig 3) No difference in fetal response was noted between primi and multigravidae nor between two women who were more than 35 years of age and the entire group

The changes in pH pCO Tc pO_2 and the energy supply between the control period and the period immediately after the end of exercise did not correlate with the changes in the incidence of irregular FBM (r = 0 22 r = 0 01 r = 0 45 and r = 0 50 respectively)

The work caused no perceptible change in the FHR when intermittently recorded The mean FHR before and immediately after the exercise was 140 ± 0 4 and 140 ± 1 3 beats per min respectively

Group II The maternal circulatory response to the exercise was similar to that of the women in Group I The maternal heart rate rose significantly from 83 to 139 beats per min during the exercise and returned successively to the control levels after 20 min The mean arterial pressure of the women increased transiently from 86 to 106 mm Hg

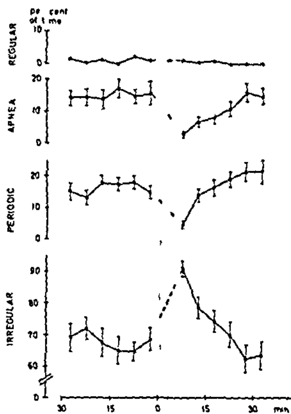
No significant difference in the basal level of the FHR or its baseline variability was detectable between the pre and post-exercise continuous recordings (Table II)

DISCUSSION

The present study demonstrated a pronounced transient increase in the incidence of FBM after a short period of moderate maternal exercise The incidence of FBM in the control period was in good agreement with that in earlier reports on normal pregnancy (12 18) The marked acute effect of moderate exercise on

Table II *Fetal heart rate (beats per min) measured continuously before and after exercise (Group II exercise period 0 5 min n = 10) FHR could not be registered during the exercise for technical reasons (see text)*

	Min from start			
Parameter	−30−0	6−10	11−15	16−20
A Fetal heart rate				
Baseline level				
mean	139	138	139	140
± SEM	± 3 2	± 2 7	± 2 7	± 2 6
Sign of diff t		0 689	0 495	0 909
p		n s	n s	n s
B Fetal heart rate				
Baseline variability				
mean	15	15	15	16
± SEM	± 0 8	± 1 0	± 1 3	± 1 3
Sign of diff t		0 165	0 263	0 780
p		n s	n.s	n s



3. Distribution of fetal breathing movement patterns ng the exercise test in 30 pregnant women (Group I ± SEM for 5 minute periods). The shaded area de the exercise period (0 5 min)

FBM in normal pregnancies is of importance in view of the fact that the work load did not affect either the basal level or the baseline variability of FHR. The present results agree well with the reports by Hon and Wohlgemuth (14) and Stembera (27) which demonstrated no or only slight FHR changes after step-test in uncomplicated pregnancies. However, Pomerance *et al* (24) showed that in 9 per cent of normal pregnant women a reduction in FHR of more than 16 beats per minute followed a bicycle ergometer test at a load level similar to ours. The present findings confirm the greater reactivity to various stimuli of FBM compared with FHR. This has also been demonstrated in human fetuses after maternal smoking (12) or in chronic distress (5). Similar results were reported from experiments on Rhesus monkeys (19) and sheep (23). Thus an abnormal pattern of FBM in lambs for 30 hours before intrauterine death was accompanied by normal FHR (23).

Clearly several factors might play a part in mediating the alteration of the FBM. The *mechanical* stimuli from the maternal muscular movements dislocating the uterus during the test and transmitted to the fetus are one possible mechanism. Boddy (6) recently reported that palpation of the uterus decreased the FBM in man whereas on the other hand tactile stimulation to fetuses of small laboratory animals (?) and painful irritation to lamb fetuses (25) excite FBM. The fetal response might be influenced by the activation of the *adrenergic nervous system* (11) and the *pituitary-adrenal axis* (1) occurring during physical strain. Thus in monkeys (20) and in sheep (25) infusion of catecholamines increased FBM and plasma levels of ACTH in the latter species have been shown to be inversely related to the incidence of FBM (4). Adaptation of the *maternal circulation* to exercise manifested by tachycardia and increased blood pressure might affect the placental perfusion by a redistribution of blood flow. It is in this context relevant to recall one of the few studies of uterine circulation performed on conscious pregnant women. Morris *et al* (21) reported that, after a decrease during the course of maternal work, an increase in total uterine blood flow above the control level occurred during the first five min after exercise. But these investigators could not differentiate between changes in myometrial and placental blood perfusion. A subsequent study on pregnant ewes has shown that a shift of blood flow from the uterine wall to the placenta was present immediately after maternal exercise (9). Such circulatory adaptions to work are possibly uncoupled by an altered *acid base balance* or changes in *blood gas tensions*. The cycling exercise caused a fall in maternal blood pH whereas the pCO_2 was virtually unchanged at the end of the exercise period. At that point the oxygenation measured as Tc pO_2 had reached its highest level. It has been demonstrated that mild hypercapnia with or without concomitant hyperoxemia decreased the porcine uterine vascular resistance (13), and isolated increase of the CO_2 tension in fetal blood stimulated to increased FBM in sheep (3). It is also of some interest to note in view of the observation that in sheep the presence of the FBM is associated with a certain pattern of the fetal electrocorticogram (10) that induced acidosis caused a decreased over all amplitude and a disappearance of fast rhytms in the electrocorticogram of fetal lambs (17).

It is not possible from the data available in the present study to clarify the mechanism(s) responsible for the transient alteration of the FBM. However this work showed that moderate exercise in normal gestation is a more powerful stimulus to the fetal

breathing system than to the cardiac centers The observation suggests that in some situations the monitoring of FBM might constitute an investigative clinical method for supervision of the fetus with a higher resolution power than hitherto offered by the study of the FHR

ACKNOWLEDGEMENTS

The authors thank Mrs Eva Eriksson Miss Ann Thuring and Mr Arne Bjuvholt for expert technical help We are grateful to colleagues from the Department of Clinical Physiology University of Lund Allmänna Sjukhuset Malmö for laboratory analysis and valuable discussions

Supported by grants from the Swedish Medical Research Council (B77 17X-04517-03) the Swedish Tobacco Company and the Medical Faculty of the University of Lund

REFERENCES

1 Bellet S Roman, L & Barham F Effect of physical exercise on adrenocortical secretion Metabolism *18* 484 1969

2 Boddy K & Robinson J S External method for detection of fetal breathing in utero Lancet *2* 1231 1971

3 Boddy K Dawes G S Fisher R Pinter S & Robinson J S Foetal respiratory movements electrocortical and cardiovascular responses to hypoxaemia and hypercapnia in sheep J Physiol *243* 599 1974

4 Boddy K Jones C & Robinson J Correlations between plasma ACTH concentrations and breathing movements in foetal sheep Nature *250* 75 1974

5 Boddy K & Dawes G S Fetal breathing Brit Med Bull *31* 3 1975

6 Boddy K Fetal circulation and breathing movements *In* Fetal physiology and medicine (eds R W Beard P W Nathanielsz) pp 302 328 W B Saunders Comp Ltd London 1976

7 Bonar B E Blumenfeld C M & Fenning C Studies of fetal respiratory movements I Historical and present day observations Am J Dis Child *55* 1 1938

8 Burton A C Physiology and Biophysics of the circulation p 86 Year Book Medical Publishers Inc Chicago 1965

9 Curet L B Orr J A Rankin J H G & Ungerer T Effect of exercise on cardiac output and distribution of uterine blood flow in pregnant ewes J Appl Physiol *40* 725 1976

10 Dawes G S Fox H E Leduc B M Liggins G C & Richards R T Respiratory movements and rapid eye movement sleep in the foetal lamb J Physiol *220* 119 1972

11 Euler U S von & Hellner S Excretion of noradrenaline and adrenaline in muscular work Acta Physiol Scand *26* 183 1952

12 Gennser G Maršál K & Brantmark B Maternal smoking and fetal breathing movements Am J Obstet Gynecol *123* 861 1975

13 Hanka R Lawn L Mills I H Prior D C & Tweeddale P The effects of maternal hypercapnia on foetal oxygenation and uterine blood flow in the pig J Physiol *247* 447 1975

14 Hon E H & Wohlgemuth R The electronic evaluation of fetal heart rate Am J Obstet Gynecol *81* 361 1961

15 Huch R Huch A & Lübbers D W Transcutaneous measurement of blood pO_2 ($tcPO_2$) method and application in perinatal medicine J Perinat Med *1* 183 1973

16 Kuhlmann G Mosler K H & Schwalm H Fetale Herzfrequenz und Wehentätigkeit nach Ergometerbelastung von gesunden Schwangeren am Tragzeitende Z Geburtsh Perinat *178* 279 1974

17 Mann L I Solomon G Carmichael A & Duchin S The effect of metabolic acidosis on fetal brain function and metabolism Am J Obstet Gynecol *111* 353 1971

18 Manning F A & Feyerabend C Cigarette smoking and fetal breathing movements Br J Obstet Gyn *83* 262 1976

19 Martin C B Murata Y Petrie R H & Parer J T Respiratory movements in fetal Rhesus monkeys Am J Obstet Gynecol *119* 939 1974

20 Martin C B Factors affecting breathing movements in fetal rhesus monkeys *In* Proceedings of the 3rd Conference on Fetal Breathing Malmö June 8 1976 (eds G Gennser K Maršál T Wheeler) pp 40-43 Malmö 1977

21 Morris N Osborn S B Wright H P & Hart A Effective uterine blood flow during exercise in normal and pre eclamptic pregnancies Lancet *2* 481 1956

22 Parmelee A H Stern E & Harris M A Maturation of respiration in prematures and young infants Neuropädiatrie *3* 294 1972

23 Patrick J E Dalton K J & Dawes G S Breathing patterns before death in fetal lambs Am J Obstet Gynecol *125* 73 1976

24 Pomerance J J Gluck L & Lynch V A Maternal exercise as a screening test for uteroplacental insufficiency Obstet Gynecol *44* 383 1974

25 Scarpelli E M Condorelli S & Cosmi E V Cutaneous stimulation and generation of breathing in the fetus Pediat Research *11* 24 1977

26 Soiva K Salmi A Grönroos M & Peltonen T Physical working capacity during pregnancy and effect of physical work tests on foetal heart rate Ann Chir Gynaecol Fenn *53* 187 1964

27 Stembera Z K Fetal tolerance to maternal exercise hypoxia *In* Perinatal factors affecting human development Scientific Publication No 185 pp 105 110 Pan American Health Organization Washington 1969

28 Sterky G Swedish standard curves for intra uterine growth Pediatrics *46* 7 1970

29 Toubas P L Monset Couchard M Rey P Predine J Verbrugge M Leandri J & Tchobroutsky C Fetal breathing and adaption to maternal haemorrhage in the sheep Am J Obstet Gynecol *127* 505 1977

Submitted for publication October 28 1977

Karel Maršál
Department of Obstetrics and Gynecology
Allmänna Sjukhuset
S-214 01 Malmö

ANNOUNCEMENT

International Symposium on Human Placenta Proteins and Hormones is to be held at the University of Siena Italy July 4–7 1979

Scientific Committee Arnold Klopper Aberdeen Scotland Pier Giorgio Crosignani Milan Italy and Andrea Genazzani Siena Italy

Sponsors C N R Project Biology of Reproduction Italian Societies of Obstetrics Gynaecology and Endocrinology Serono Symposia Biodata

Topics

- New placental proteins chemistry assay biological and clinical significance
- Newly discovered placental β-endorphin
- Physiology in mother and fetus of placental protein and steroid hormones
- Correlations between morphology and endocrine placental activity
- Physiological variability of endocrine indices
- Placental provocative tests

  Integrated use of endocrine and physical parameters in clinical practice
- Mechanism involved in the initiation of labor
- Lactogenic hormones and mammary gland during pregnancy and post partum

Round Table Clinical use of endocrine indices critical evaluation

Invited Speakers

M Aubert Geneva Switzerland P Bischof Aberdeen Scotland H Bohn Marburg F R Germany T Chard London England P Crosignani Milan Italy G De Virgilus Milan Italy F Fraioli Rome Italy F Fuchs New York U S A A Genazzani Siena Italy P Keller Zürich Switzerland A Klopper Aberdeen Scotland A Liotta New York U S A G Mandruzzato Trieste Italy C Robyn Brussels Belgium A Scommegna Chicago U S A Y Tatarinov Moscow USSR A C Turnbull London England G R Wilson Aberdeen Scotland

Official languages English and Italian

Researchers are invited to submit 250 word abstracts of unpublished work for oral or poster presentation before April 15 1979 A limited number of free communications will be selected for presentation and published with the invited lectures in the proceedings by Academic Press Abstracts of invited lectures free communications and posters will be published in a separate volume

Scientific Secretary

Professor A R Genazzani

Cattedra di Patologia Ostetrica e Ginecologica

Via Paolo Mascagni 46

53100 SIENA Italy

Tel 0557/49206 44051

International Symposium on Adrenal Androgens is to be held at the University of Siena Italy October 7 9 19[illegible]

Scientific Committee A R Genazzani Siena Italy C Giusti Florence Italy P C MacDonald Dallas USA W D Odell Torrance U S A P K Siiteri San Francisco U S A J H H Thijssen Utrecht Holland A Vermeulen Ghent Belgium

Sponsors The American Express Company under the auspices of the Italian Society of Obstetrics and Gynaecology the Italian Society of Endocrinology the Italian Society of Fertility and Sterility and the C N R project Biology of Reproduction

Topics

- Androgen secretion by human adrenal and testis cells in culture
- Hormonal factors controlling and stimulating adrenal androgen secretion
- Adrenal androgen metabolism and conversion in human[illegible]
- Adrenal androgens in pregnancy in prepuberty [illegible] adult life ageing and in postmenopausal women [illegible] and obsese subject
- Enzymatic adrenal factors
- Adrenal androgens and endometrial cancer

  Adrenal androgen effects on bone metabolism and on the hypothalamus pituitary gonadal axis

Round Table Adrenal androgens the future

Invited Speakers G Abraham Rolling Hills U S A D Anderson Manchester England A Genazzani Siena Italy G Giusti Florence Italy P MacDonald Dallas U S A A Neville Sutton England B Nordin Leeds England W Odell Torrance U S A C Pinto Cagliari Italy J Poortman Utrecht Holland M Serio Florence Italy P Siiteri San Fransisco U S A P Sizonenko Geneva Switzerland J Thijssen Utrecht Holland D Tchinsky Boston U S A A Vermeulen Ghent Belgium

Official language English

Researchers are invited to submit 250 word abstracts of unpublished work for oral or poster presentation before [illegible] 15 1979 A limited number of free communications will be selected for presentation and published with the invited lectures in the proceedings Abstracts of invited lectures free communications and posters will be published in a separate volume

Scientific Secretary

Professor A R Genazzani

Centro di Fisiopatologia della Riproduzione

Università di Siena

Via Paolo Mascagni 46

53100 SIENA Italy

Tel 0577/49206 44051

Acta Obstet Gynecol Scand 58 203–207 1979

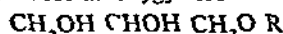
EFFECT OF ALKOXYGLYCEROLS ON THE FREQUENCY OF FISTULAS FOLLOWING RADIATION THERAPY FOR CARCINOMA OF THE UTERINE CERVIX

Astrid Brohult Johan Brohult Sven Brohult and Ingemar Joelsson

From the Clinical Laboratory and the Department of Gynecology Radiumhemmet the Department of Internal Medicine IV Sodersjukhuset the Royal Academy of Engineering Sciences Stockholm and the Department of Obstetrics and Gynecology University of Umeå Umea Sweden

Abstract The incidence of injuries following radiation therapy for carcinoma of the uterine cervix is markedly decreased by the administration of alkoxyglycerols This is the case for less harmful injuries as well as for the more severe ones i e the fistulas Recto vaginal and vesico-vaginal fistulas are reduced with 47 per cent when alkoxyglycerols are administered prior to to radiation treatment

Alkoxyglycerols occur in small quantities in several natural products They are relatively abundant in the heamopoietic organs of mammals particulary the bone marrow These substances also occur in relatively high concentrations in the human mother s milk They occur most abundantly however in the liver oil of certain species of shark These oils contain up to 50 per cent of alkoxyglycerol esters (1 9 10) The general formula for alkoxygylcerols is



$$CH_2OH\ CHOH\ CH_2O\ R$$

where R is a long-chain aliphatic radical The most common natural sources are the saturated batyl and chimyl alcohols (with 18 and 16 carbon atoms respectively in the side chain) and the unsaturated selachyl alcohol with 18 carbon atoms in the side chain

The alkoxyglycerols have proved to be of medical interest (1 8) The administration of alkoxyglycerols before during and after radiation treatment reduces to a large extent (ca 50 per cent) the frequency of injuries following radiation therapy (5 7)

The aim with the present study has been to investigate the incidence of severe injuries (i e vesico-vaginal and recto vaginal fistulas) following radiotherapy for carcinoma of the uterine cervix Problems connected with the development of radiation tissue damage following radiotherapy have earlier been elucidated in several publications from the Radiumhemmet in Stockholm where all patients included in the present study received their treatment (11 12 14 15 16 17)

MATERIAL AND METHODS

The clinical experiments in this study have been conducted using alkoxyglycerol preparations from the liver oil of the Greenland shark The preparation produced by AB Astra with the working name AT 18 is a concentrate containing 85 per cent free alkoxygylcerols

The alkoxyglycerols were administered orally in capsules 2 capsules 3 times a day each capsule containing 0 1 g of alkoxyglycerols The total daily dosage thus was 0 6 g

The series of cases with invasive carcinoma of the uterine cervix treated at the Department of Gynecology Radiumhemmet Stockholm were reviewed during various periods The patients were allotted to one of the following groups

I Patients given alkoxyglycerols prophylactically i e during 7 days before during the treatment period and for 1 3 months after the completion of radiotherapy

II Patients given alkoxyglycerols only during the period of radiotherapy and for 1 3 months thereafter non prophylactic administration

III Patients given solely radiotherapy

Groups I II and III cases were studied during the time period 1963 1966 category A Group I and III cases were studied also 1970 1972 category B 99 per cent of the patients treated for carcinoma of the uterine cervix during the period January 1 1964 February 15 1966 received alkoxyglycerols either prophylactically or as non prophylactic administration These patients are enclosed in groups I and II of category A Patients within group III of category A were treated during 1963 (348 patients) and February 16-December 31 1966 (309 patients) A double blind study comprising 279 patients was conducted 1970 1972 These patients form Group I and III of category B While category A patients have been followed for more than 5 years the category B patients have been followed up for 3 5 years from the initiation of therapy

The treatment was in almost all cases initiated with intracavitary radium application followed by external radiotherapy For data regarding radiation treatment the reader is referred to previously published reports (12 13)

In the calculation of the incidence of radiation injuries in the bladder rectum ureters and small intestine the principles given by Kottmeier and Gray have been used in this investigation (17 16 11)

In earlier follow up studies regard has only been paid to injuries due to radiation (R) In this study however the in

Table I *Injuries following radiation therapy according to type of injury and grade of severity*
I = total injuries R = injuries due to radiation treatment C = complex injuries due to tumor growth or to a comb a n of tumor growth and radiation treatment

Group	No of pats	I						R						C					
		Grade II		Grade III		Grade IV		Grade II		Grade III		Grade IV		Grade II		Grade III		Grade IV	
		No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
A 1963-1966																			
I[a]	454	41	9 0	26	5 7	16	3 5	32	7 1	17	3 7	10	2 2	9	2 0	9	2 0	6	1 3
II[b]	380	48	12 6	29	7 6	16	4 2	24	6 3	7	1 8	3	0 8	24	6 3	22	5 8	13	3 4
III[c]	648	156	24 1	46	7 1	42	6 5	112	17 3	18	2 8	20	3 1	44	6 8	28	4 3	22	3 4
B 1970 1972																			
I[a]	137	26	19 0	5	3 7	5	3 7	21	15 3	2	1 5	5	3 7	5	3 7	3	2 2	–	–
III[c]	142	49	34 5	16	11 3	9	6 3	26	18 3	10	7 0	4	2 8	23	16 2	6	4 2	5	3 5

[a] Administration of alkoxyglycerols *prophylactically* and *during* radiation treatment
[b] Administration of alkoxyglycerols *only during* radiation treatment
[c] Radiation treatment only

juries due to tumor growth and to the combination of radiation tissue damage and residual or recurrent tumor growth have been considered in addition to the pure radiation injuries These injuries are called complex injuries (C) The sum of the injuries (R + C) is defined as the total number of injuries (I) Furthermore figures for the incidence of occur of more than one injury per patient i e multiple in (M) are given

Injuries have been classified according to the follow schedule given by Kottmeier (17)

Grade I Injuries producing mild subjective symptoms accompanied by minimal objective changes in the mucosa These injuries are considered as radiation reactions and have consequently been omitted

Grade II Injuries which are composed of moderately severe objective changes such as areas of necrosis ulcers or moderate stenosis

Grade III Bladder and ureter injuries comprising fistulas and rectal and intestinal injuries comprising stenoses that require colostomy

Grade IV Rectal and intestinal fistulas

Injuries which appear within three months of surgery plus radiotherapy have been excluded and those injuries which are not clearly related to the radiation treatment or to tumor growth have also been omitted Only the injuries which appear within 5 years after the onset of radiation treatment have been taken into consideration in this investigation Patients with complex injuries (C) have clinically detectable cancer residual cancer or recurrent tumor growth confirmed by biopsy or a topsy

RESULTS

Effect of alkoxyglycerols on the different grades of injuries As a supplement to the earlier presentation of the effect of alkoxyglycerols the effect of these agents on the different grades of injuries has now been analysed (Table I) In category A a sufficient n mber of patients for a valid statistical analysis is being found The results within category B with only a few patients in the various subgroups are similar to the results in category A It is observed that

1 The incidence of total grade II injuries (I grade II) is 9 per cent in the prophylactic group and 24 per cent in the control group i e a reduction with 6 per cent
2 The incidence of grade II radiation injuries (R grade II) is considerably reduced while virtually no effect is observed on radiation injuries of grade III and IV
3 The complex injuries of all grades are markedly reduced
4 In the ' non prophylactic group the radiation injuries are reduced while the incidence of the complex injuries remain the same

Incidence of fistulas following radiation therapy It is of special interest to study the effect of alkoxyglycerols on the incidence of fistulas following radiation therapy The fistulas have been separately collected and the figures are given in Table II Bladder injuries of grade III and rectal injuries of grade IV are fistulas It is observed that

1 The total number of fistulas [I grade (III + IV)] is considerably lower in the prophylactic group I than in the control group III (6 2 per cent compared with 11 6 per cent)
2 The fistulas belonging to the complex injury group [C grade (III + IV)] have decreased to 2 9 per cent

Table II *Incidence of fistulas following radiation therapy*
I = total fistulas R = fistulas due to radiation treatment C = complex fistulas due to tumor growth or to a combination of tumor growth and radiation treatment

Group	No of pats	I (fistulas)						R (fistulas)						C (fistulas)					
		Bladder		Rectal		Total		Bladder		Rectal		Total		Bladder		Rectal		Total	
		No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
A 1963-1966																			
I	454	12	2 6	16	3 5	28	6 2	5	1 1	10	2 2	15	3 3	7	1.5	6	1 3	13	2 9
II[b]	380	20	5 3	16	4.2	36	9.5	2	0 5	3	0 8	5	1 3	18	4 7	13	3 4	31	8 2
III	648	33	5 1	42	6 5	75	11 6	8	1 2	20	3 1	28	4 3	25	3 9	22	3 4	47	7 3
B 1970 1972																			
I	137	3	2 2	5	3 7	8	5 8	—	—	5	3 7	5	3 7	3	2 2	—	—	3	2.2
III	142	7	4 9	9	6 3	16	11 3	1	0 7	4	2 8	5	3 5	6	4 2	5	3 5	11	7 8

Administration of alkoxyglycerols *prophylact cally* and *during* radiation treatment
[b] Administration of alkoxyglycerols *only during* radiation treatment
Radiation treatment only

compared with 7 3 per cent

3 The pure radiation fistulas but not the fistulas of comlex origin are decreased in number in the non prophylactic group

The same results are obtained for the patients in cluded in category B but the number of fistulas is too small for a valid comparison

DISCUSSION

For the sake of comparison we have included the re sults from an earlier publication (7) in which the in juries following radiation therapy have been charac t rized as injuries due to radiation treatment (*R*) and injuries on the basis of tumor growth or a combina tion of tumor growth and radiation treatment (*C*) The main result can be briefly summarized as follows the incidence of injuries in the prophylactic group (*I* group I) was reduced with about 50 per cent and the complex injuries in the same group (*C* group I) with about 65 per cent when compared with the con trol group (group III) In the non prophylactic group (group II) no effect was observed on the incidence of complex injuries while a significant decrease was found for the injuries judged to be due to radiation solely Table III These over all results are mirrored very closely by the analysis of specific subgroups pre sented now

As there is always a certain degree of subjectivity in the interpretation of injuries following radiation treatment it has been considered of interest to analyse the effect of alkoxyglycerol treatment on the injuries divided by grade of severity Especial interest has been focused on the bladder injuries grade III and the rectal injuries grade IV i e the fistulas because an in jury of this degree can not be misinterpreted The re sult of the analysis shows that the effect of alkoxy glycerols on fistula formation is similar to the effect on injuries in general a marked effect on the total in cidence of fistulas with a greater effect on fistulas on the basis of radiation injury and suspect tumor growth in combination (*C*) than on pure radiation fistulas (*R*)

These results are mainly based on retrospective a nalysis of patient materials The results in the small randomized series of patients point however in the same direction

It should be recalled that taking only radiation in juries (*R*) into consideration these injuries are in most cases healed after a period of 6-12 months Even if the radiation injuries are painful for the patient they have only a marginal effect on the survival rate Considering on the other hand patients with com plex injuries one faces a different situation almost all of these patients are dead (98-100 %) within five years These complex injuries are reduced to one third when alkoxyglycerols are given prophylactically in comparison with the patients who received radia tion therapy only

Grade III bladder and grade IV rectal injuries are the fistulas They are reduced from 11 6 per cent to 6 2 per cent by the prophylactic alkoxyglycerol ad

Table I *Injuries following radiation therapy according to type of injury and grade of severity*
I = total injuries R = injuries due to radiation treatment C = complex injuries due to tumor growth or to a comb of tumor growth and radiation treatment

Group	No of pats	I						R						C					
		Grade II		Grade III		Grade IV		Grade II		Grade III		Grade IV		Grade II		Grade III		Grade IV	
		No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%	No	%
A 1963 1966																			
I[a]	454	41	9 0	26	5 7	16	3 5	32	7 1	17	3 7	10	2 2	9	2 0	9	2 0	6	1 3
II[b]	380	48	12 6	29	7 6	16	4 2	24	6 3	7	1 8	3	0 8	24	6 3	22	5 8	13	3 4
III[c]	648	156	24 1	46	7 1	42	6 5	112	17 3	18	2 8	20	3 1	44	6 8	28	4 3	22	3 4
B 1970 1972																			
I[a]	137	26	19 0	5	3 7	5	3 7	21	15 3	2	1 5	5	3 7	5	3 7	3	2 2	–	–
III[c]	142	49	34 5	16	11 3	9	6 3	26	18 3	10	7 0	4	2 8	23	16 2	6	4.2	5	3 5

[a] Administration of alkoxyglycerols *prophylactically* and *during* radiation treatment
[b] Administration of alkoxyglycerols *only during* radiation treatment
[c] Radiation treatment only

juries due to tumor growth and to the combination of radiation tissue damage and residual or recurrent tumor growth have been considered in addition to the pure radiation injuries These injuries are called complex injuries (C) The sum of the injuries (R + C) is defined as the total number of injuries (I) Furthermore figures for the incidence of occur of more than one injury per patient i e multiple in (MI) are given

The injuries have been classified according to the follow e given by Kottmeier (17)

Grade I *Injuries producing mild subjective symptoms accompanied by minimal objective changes in the mucosa These injuries are considered as radiation reactions and have consequently been omitted*

Grade II Injuries which are composed of moderately severe objective changes such as areas of necrosis ulcers or moderate stenosis

Grade III Bladder and ureter injuries comprising fistulas and rectal and intestinal injuries comprising stenoses that require colostomy

Grade IV Rectal and intestinal fistulas

Injuries which appear within three months of surgery plus radiotherapy have been excluded and those injuries which are not clearly related to the radiation treatment or to tumor growth have also been omitted Only the injuries which appear within 5 years after the onset of radiation treatment have been taken into consideration in this investigation Patients with complex injuries (C) have clinically detectable cancer residual cancer or recurrent tumor growth confirmed by biopsy or autopsy

RESULTS

Effect of alkoxyglycerols on the different grades of injuries As a supplement to the earlier presentation of the effect of alkoxyglycerols, the effect of these agents on the different grades of injuries has now been analysed (Table I) In category A a sufficient number of patients for a valid statistical analysis is being found The results within category B with only a few patients in the various subgroups are similar to the results in category A It is observed that

1 The incidence of total grade II injuries (I grade II) is 9 per cent in the prophylactic group and 24 per cent in the control group i e a reduction with 6 per cent
2 The incidence of grade II radiation injuries (R grade II) is considerably reduced while virtually no effect is observed on radiation injuries of grade III and IV
3 The complex injuries of all grades are markedly reduced
4 In the " non prophylactic group the radiation injuries are reduced while the incidence of the complex injuries remain the same

Incidence of fistulas following radiation therapy It is of special interest to study the effect of alkoxyglycerols on the incidence of fistulas following radiation therapy The fistulas have been separately collected and the figures are given in Table II Bladder injuries of grade III and rectal injuries of grade IV are fistulas It is observed that

1 The total number of fistulas [I grade (III + IV)] is considerably lower in the prophylactic group than in the control group III (6 2 per cent compared with 11 6 per cent)
2 The fistulas belonging to the complex injury group [C grade (III + IV)] have decreased to 2 9 per cent

13 Joelsson I & Bäckström A Dose rate measurements in bladder and rectum Acta Radiol Ther Phys Biol *8* 343 1969

14 Joelsson I Räf L & Söderberg G Stenosis of the small bowel as a complication in radiation therapy of carcinoma of the uterine cervix Acta Radiol Ther Phys Biol *10* 593 1971

15 Kottmeier H L Carcinoma of the Female Genitalia The Abraham Flexner Lectures Series No 11 The Williams & Wilkins Co Baltimore 1953

16 Kottmeier H L & Gray M J Rectal and bladder injuries in relation to radiation dosage in carcinoma of the cervix A five year follow up Am J Obstet Gynecol *82* 74 1961

17 Kottmeier H L Complications following radiation therapy in carcinoma of the cervix and their treatment Am J Obstet Gynecol *88* 854 1964

Submitted for publication Nov 22 1977

Astrid Brohult
Clinical laboratory
Radiumhemmet
S-104 01 Stockholm
Sweden

ANNOUNCEMENT

A European Congress of Obstetric Anaesthesia and Analgesia will take place at the Birmingham Metropole Hotel adjacent to the National Exhibition Centre from the 17th to the 20th September 1979

Further details may be obtained from
Dr J Selwyn Crawford Consultant Anaesthetist
Birmingham Maternity Hospital
Edgbaston
Birmingham B15 2TG
England

An International Congress on *Interdisciplinary* [illegible] *Diseases of the Female Breast* will take place in [illegible] May 27 31 1980 organized by the Senologic [illegible] Society

Themes of Congress

Benign and malign diseases of the female breast [illegible] etiology endocrinology histopathology [illegible] prognosis therapy

Direct Inquires to
Professor Dr H J Frischbier
Universitäts Frauenklinik
Martinistrasse 52
200 Hamburg 20
Germany

Acta Obstet Gynecol Scand 58 209–210 1979

SHORT COMMUNICATION

EXTERNAL CEPHALIC VERSION IN THE MANAGEMENT OF BREECH PRESENTATION WITH SPECIAL REFERENCE TO THE PLACENTAL LOCATION

Stefan Fianu and Vlasta Václavinková

From the Department of Obstetrics and Gynecology Karolinska Institutet Sabbatsberg Hospital Stockholm Sweden

As a consequence of a preliminary study (2) it has been suggested that the fetus accommodates itself to the shape of the amniotic sac the smaller fetal pole occupying the smaller pole of the sac and vice versa Thus a cornuo fundally implanted placenta reducing the upper pole of the amniotic sac may render attempts at external version unsuccessful

MATERIAL AND METHODS

In a series of 74 primary breech presentations regularly followed up at the antenatal care unit at the University Department of Obstetrics and Gynecology at Sabbatsberg Hospital in Stockholm during the period January 1976–December 1977 the result of attempts at cephalic versions were studied

Roentgenologic pelvimetry prenatal estimation of the fetal weight and placental localization by ultrasonography were carried out in all the patients examined representing cases from consecutive hospital admissions Only pregnan complicated by some disorder in either mother or child e g placenta praevia contracted pelvis accidental hemorrhage toxemia elderly primipara and cases when elective cesarean section was intended have been excluded External version was attempted when the fetus presented as a breech in patients of 35 (or more) weeks of gestation There were 39 primiparae and 35 multiparae

All the 74 attempts at external version were made without anesthesia and in each case only one attempt was performed No maternal or fetal death followed the attempted versions In no case did spontaneous version take place after the attempted version

To analyze satisfactorily the results obtained in this series the breech presentations have been divided into two groups according to the localization of the placenta In Group I the placenta was located in one of the cornuo-fundal regions while in Group II it was located on the anterior or posterior wall of the uterus

RESULTS

The incidence of successful or temporarily successful version in this series of 74 cases was 65 per cent This is similar to the results reported by others (1 3 4 5) The overall incidence of successful versions in Group I (placenta located in one of the cornu–fundal region) was 44 4 per cent compared with 96 6 per cent in Group II (placenta located on the anterior or posterior wall of the uterus)

It is interesting to note that there were no reversions in Group II while seven cases reverted following *initial success (35 per cent) in the first group* The overall reversion rate was 14 6 per cent (Table) No complication occurred in any of the 41 cases of successful version and all were delivered vaginally in vertex presentation

Table I *Results of external cephalic version with reference to the placental position*

Location of placenta	Successful versions No	Successful versions %	Failed attempts No	Failed attempts %	Reversion No	Reversion %	Total No	Total %
Cornuo-fundal implantation	20	44 4	25	55 6	7	35 0	45	60 8
Implantation on the anterior or posterior uterine wall	28	96 6	1	3 4	—	—	29	39 2
Total	48	64 9	26	35 1	7	14 6	74	—

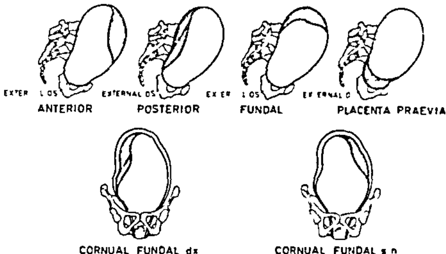


Fig 1 Placental site classified into six main groups

CONCLUSION

The practice of external version as a prophylactic measure in the obstetrical care of breech presentations seems to be more successful if the placenta is located anteriorly rather than in one of the cornuofundal regions It is therefore suggested that placenta localization with ultrasound is performed prior to version In properly selected cases external version can be done with a minimum of risk to the mother and the fetus

REFERENCES

1 Beischer N A and Townsend L External cephalic version in breech presentation J Obstet Gynecol Brit Emp 67 (1960) pp 668 671
2 Fianu S and Václavinková V The site of placental attachment as a factor in the aetiology of breech presentation Accepted for publication in Acta Obstet Gynecol Scand
3 Kuhnel P Active versus conservative technique in breech delivery and the prophylactic value of external version in pregnancy Acta Obstet Gynecol Scand 33 (1954)
4 Ranney B The gentle art of external cephalic version Am J Obstet Gynecol *116* 239 1973
5 Ryder G H Breech presentations treated by cephalic versions in the consecutive deliveries of 1700 women Am J Obstet Gynecol *45* 1104 1943

Submitted for publication March 3 1978

Stefan Fianu M D
Department of Obstetrics and Gynecology
Sabbatsberg Hospital
S-113 8 Stockholm
Sweden

Acta Obstet Gynecol Scand 58 211–212 1979

SHORT COMMUNICATION

PLASMA PROGESTERONE CONCENTRATIONS AFTER ADMINISTRATION VIA INTRAVAGINAL RINGS

Torbjörn Bäckström Bo von Schoultz and Juhani Toivonen

From the Departments of Physiology and Obstetrics and Gynecology University of Umeå Umea Sweden and the Steroid Research Laboratory
Department of Medical Chemistry University of Helsinki Helsinki Finland

The main reason for the frequent use of synthetic progestins instead of natural progesterone for hormonal treatment is the lack of suitable administration routines for the native hormone Intramuscular injections must be repeated daily to maintain adequate plasma levels (1) Suppositories and vagitories have been tried (1) but the concentrations in plasma following their administration were not stable Intravaginal rings (IVR) homogeneously impregnated with various progestins have produced high but declining plasma levels (2 3) Recently more constant plasma concentrations were reported in studies using rings containing a core impregnated with progesterone (4) Values were low between 0 5 and 2 5 ng/ml but remained stable for several cycles (4) The present study was performed to confirm these data and to see if higher plasma concentrations could be obtained by using rings where the core contained maximal amounts of progesterone

EXPERIMENTAL

The IVR s were made of silicone polymer polysiloxane (silastic 387 Medical Grade Elastomer Dow Corning Corp Medical Products Division Midland Michigan USA) containing 708 ± 4 7 (mean±SD) mg of progesterone in the polysiloxane core of the ring The outer diameter of the rings was 60 mm and the thickness 9 mm Eight apparently healthy women mainly form the hospital staff aged 22 to 39 years with regular cycles volunteered for the study The IVR was inserted in the morning on day 5 of the cycle Blood samples were taken on day 4 5 (before IVR insertion and five hours after IVR insertion) 6 7 9 11 13 16 19 and 22 All samples were taken in the morning Plasma progesterone was assayed in triplicate samples using a direct radioimmunoassay described earlier (5)

RESULTS AND COMMENTS

The mean maximal plasma concentration of progesterone was 4 4 ng/ml (range 2 4-6 5 ng/ml) which was obtained in the afternoon on the day of insertion (Fig 1) The mean level was then quite stable and during the first eight days the mean decline was only 0 14 ng/day At the end of the investigation period the mean concentration increased probably due to an endogenous production of progesterone Thus it seems that the ovulation was not inhibited in all women Five individual concentration curves are given in Fig 2 Four of the eight women had spottings during the study but on the whole the IVR s were well ac

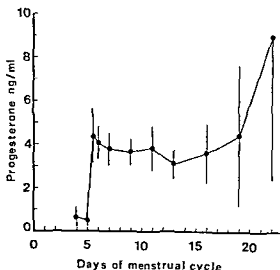


Fig 1 Mean ±SD of plasma progesterone in eight women after administration via intravaginal rings during the follicular phase

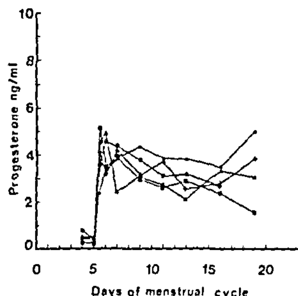


Fig 2 Examples of individual concentrations of plasma progesterone after administration via intravaginal rings

cepted both by the women and their partners The plasma concentrations in this study being twice those previously obtained (4) almost equals the values during the early luteal phase The rings were expected to ve a constant release for at least 90 days and the se concentrations were low compared to the high a nts of progesterone in the core When 100 mg of gesterone was administered in vagitories made of cocoa fat Nillius and Johansson (1) found maximal concentrations around 10-20 ng/ml followed by a rather rapid decrease probably due to a rapid release of the whole amount of steroid Homogeneously impregnated rings as used by Viinika *et al* (2) and Victor *et al* (3) in their earlier studies also gave a rapid release of steroid from the surface of the ring In the present study the initial high burst in release was almost completely eliminated Therefore these r g might be used in studies or therapy where sta[illegible] plasma levels of progesterone are required

ACKNOWLEDGEMENTS

This work was supported by Swedish Med al Resea[illegible] Council (project 14X-05 03) K O Hansso[illegible] s a[illegible] berg s funds and Gunvor and Josef Anérs S[illegible] Birgitta Wikström is acknowledged for skilful tech[illegible] assistance

REFERENCES

1 Nillius S J & Johansson E D B Plasma levels of progesterone after vaginal rectal or intramuscular administration of progesterone Am J Obstet Gynecol *110* [illegible] 1971
2 Viinikka L Victor A Jänne O & Raynau[illegible] The plasma concentration of a synthetic proges[illegible] 2323 released from polysilastic vaginal rings Contraception *12* 309 1975
3 Victor A Edqvist L E Lindberg P Elam[illegible] K & Johansson E D B Peripheral plasma levels of d Norgestrel in women after oral administration of d Norgestrel and when using intravaginal rings impregnated with d Norgestrel Contraception *12* 61 1975
4 Toivonen J Lahteenmäki P & Luukkainen T Plasma steroid and gonadotropin profiles during the treatment with progesterone releasing vaginal rings (to be published)
5 Bäckström T & Carstensen H Estrogen and progesterone in plasma in relation to premenstrual tension J Steroid Biochem *5* 257 1974

Submitted for publication May 23 19 8

Torbjörn Bäckström M D
Department of Physiology
University of Umeå
S-901 87 Umeå
Sweden

Acta Obstet Gynecol Scand 58 213–214 1979

SHORT COMMUNICATION

OESTROGEN RECEPTORS IN DYSPLASTIC AND MALIGNANT VULVAL TISSUE

R Johansson M Gronroos I Kouvonen and T Lovgren

From the Department of Obstetrics and Gynaecology and the Department of Radiotherapy University of Turku and the Department of Biochemistry and Pharmacy Åbo Akademi Turku Finland

The physiological development and maintenance of the vulval region is under the control of steroid sex hormones Accordingly senile atrophy and some more or less premalignant lesions are treated with a great variety of topical drugs of which the commonest are cortisone and oestrogen preparations It has been shown that tissues and cells which respond to steroid hormones contain specific proteins which are capable of binding the specific steroid with a high affinity but low capacity

It was our aim to look for such proteins in the vulva in benign dysplastic and malignant lesions and to correlate these to the normal skin from other parts of the body

The method used is the same as used for determining oestrogen receptors in mammary and uterine cancer tissues—the dextran coated charcoal method (3) The chief steps of the method are as follows an immediate cooling of the sample on ice and homogenisation in an ice bath preparation of the cytosol fraction by high speed centrifugation incubation of the soluble cytosol fraction with radioactive oestrogen with or without an excess of non radioactive oestrogen and finally the radioactive hormone bound to the protein was separated from the free hormone by dextran coated charcoal The dissociation constant and binding capacity were determined graphically according to Scatchard

The study consisted of eleven patients 27–69 years old of whom three had an invasive vulval carcinoma one had an intraepithelial carcinoma (Mb Bowen) three had a vulval kraurosis (lichen sclerosus et atrophicus) and four patients with apparently normal vulva for control The diagnoses were histologically verified from a biopsy taken with the help of colposcopy and phosphorus scanning (1 2) For the purpose of the present investigation samples were taken as follows one sample from the most affected region of the vulva a second sample from an apparently benign region of the vulva and a third sample from the skin of the thigh In the control patients only one sample from the vulva and one sample from thigh were taken

All the samples from the thigh showed a specific binding capacity of 2–6 fmol/mg cytosol protein The samples from the benign vulval tissue (both in the control patients and in the patients with vulval lesions elsewhere) showed binding values of 4–9 fmol/mg cytosol protein The binding of vulval dysplastic or cancerous tissue showed a binding capacity of 3–9 fmol/mg cytosol protein

There was no difference in the binding capacities between the normal dysplastic and cancerous areas of the vulva nor the skin of the thigh All these binding capacities were relatively low for in comparison the receptor positive mammary cancer samples bind 20–200 fmol/mg cytosol protein The dissociation constants however were of the same order of magnitude (0 15–0 95 nM) which shows that the determined proteins were receptors

It is well known that oestrogens in atrophic vulvovaginitis and cortisone in vulval kraurosis give fairly good results and that during the pregnancy the kraurotic changes may disappear These facts suggest a hormonal dependency The present investigation shows that benign dysplastic and malignant vulval superficial tissue contains oestrogen re

ceptors although only in sm ill amounts Clinical experience shows however that even this is enough to mediate the effect of oestrogens

REFERENCES

1 Grónroos M Lindgren I Laakso I & Vilhonen E ^{32}P uptake in vulval dysplastic and malignant epi thelium Ann Chir Gynaecol Fenn 56 118 1969
2 Punnonen R Gronroos M & Lindgren I The value of ^{32}P in the diagnosis of various vulval lesions Gynecol Oncol 5 187 1977
3 Punnonen R Kouvonen I Lövgren T & Rauramo I Uterine and ovarian oestrogen receptor levels in climacteric women Acta Obstet Gynecol Scand in press

Submitted for publication April 24 19 5

Risto Johansson
Department of Radiotherapy
University of Turku
SF 05 0 Turku 5
Finland

Acta Obstet Gynecol Scand 58 215–216 1979

CASE REPORT

FAILURE OF FUSION BETWEEN AN UPPER AND A LOWER SEGMENT OF THE VAGINA

Mogens Ingerslev
From the University Department of Obstetrics and Gynecology the Municipal Hospital Århus Denmark

Abstract A unique malformation of the vagina with a tiny fistula between an upper and a lower segment of the vagina is presented with a brief summary of the theories concerning the development of the vagina

The development of the vagina is not yet finally clarified Recently a patient with failure of fusion between an upper and a lower segment of the vagina was seen in this department This case may elucidate some of the problems related to the development of the lower part of the genital tract

CASE HISTORY

A ?1 year-old woman (S L 070256) was referred to this department complaining of dyspareunia She had always been healthy Her menstrual periods were regular (5 days/28–30 days) with slight dysmenorrhoea Attempts at coitus had failed apparently due to narrowness of the vagina

Her general appearance including the external genital organs was perfectly feminine By vaginal examination a horizontal 1–2 cm broad band was found 1 cm above the remnants of the hymen The band was divided and a 5 cm deep vagina with a diameter of 2 5 cm was seen The upper end of the vagina showed no signs of a cervix and the epithelium was apparently intact

When seen during the following menstrual period a tiny fistula was localized in the posterior wall 1 cm below its apex The fistulous tract which was about 1 cm long was dilated giving access to a vagina with a diameter of 3 cm and a length of 5–6 cm with a perfectly normal cervix at the top

Due to secondary shrinkage of the fistulous area a repeat dilatation was performed 3 months later with excision of a valve like membrane Histological examination of the specimen removed showed a normal vaginal epithelium above as well as below the fistulous area

DISCUSSION

It has proved difficult to determine by morphological studies whence the vagina and its epithelium derive Four different theories existed even in the nineteenth century

1 1830 Johannes Muller (1) described the ducts that have since borne his name and stated that the vagina developed from the ducts

2 1967 Furst (2) suggested that most of the vagina developed from the Mullerian ducts

3 1884 Pozzi (3) agreed that the major of the vagina is formed by the Mullerian ducts although a small part cranial to the hymen originates from the urogenital sinus

4 1884 Tourneux & Legay (4) claimed that the sino vaginal bulbs are formed by epithelium from the caudal part of the Wolffian ducts and not as usually stated by invagination from the urogenital

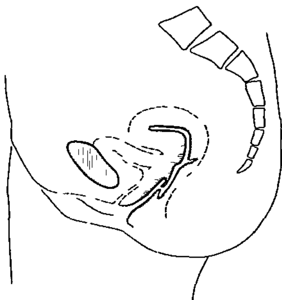


Fig 1 A sketch of the genital tract of a unique case with an upper and a lower segment of the vagina communicating by a tiny fistula

sinus Accordingly they found that the epithelium of the Wolffian ducts is involved in the formation of the lower part of the vagina

An extensive survey of the literature has been presented by Forsberg in 1963 (5) From this excellent survey it is apparent that the development of the vagina is a question not yet solved in spite of numerous morphological and histological studies

The problem has been approached in a different way by studying various congenital malformations of the vagina The occurrence of a perfect duplication of the vagina may indicate that the vagina arises solely from the Mullerian ducts A rudimentary vagina may however be seen in patients with aplasia of the vagina and a more or less hypoplastic vagina is quite often present in cases with male hermaphroditism This may prove that a vagina although imperfect can develop from the urogenital sinus Finally a malformation of the unique type presented here indicates that the lower part of the vagina may develop from the urogenital sinus in the presence of an apparently normal upper segment arising from the caudal part of the Müllerian ducts

some respects observations based on malfor of the genital tract may be more informative than morphological and histological s[illegible] However the types of malformations [illegible] here are not a proof but only an indication th[illegible] normal vagina may be formed partially from the caudal part of the Müllerian ducts and partially from the urogenital sinus

REFERENCES

1 Müller J Bildungsgeschichte der Genitalien Arn[illegible] Comp Düsseldorf 1830
2 Fürst L Über Bildungshemmungen des [illegible] Vaginalkanales Ms hr Geburtsk (Berlin) 30 9[illegible] 18[illegible]
3 Pozzi S De la bride masculine du ves[illegible] chez la femme Ann Gynécol 21 268 1884
4 Tourneux F & Legay C Mémoire sur le développement de l utérus du vagin J Anat 20 330 1884
5 Forsberg J -G Derivation and differentiation of the vaginal epithelium Lund 1963

Submitted for publication March 2 1978

Mogens Ingerslev
Department of Obstetrics and Gynecology
The Municipal Hospital
Århus
Denmark

Acta Obstet Gynecol Scand 58 217–220 1979

CASE REPORT

ULTRASONOGRAPHIC DIAGNOSIS OF FETAL ASCITES IN A TWIN PREGNANCY

Z Weinraub R Langer I Bukovsky D Schneider
and E Caspi

*From the Department of Obstetrics and Gynecology Ultrasonographic Sub Unit
Asaf Harofe Government Hospital University of Tel Aviv Medical School
Zerifin Israel*

In the last two decades ultrasonographic examinations have become a useful noninvasive diagnostic tool in various obstetric conditions A case is described where fetal ascites due to Rh isoimmunisation in a twin pregnancy was antenatally diagnosed by means of B scan technique To our knowledge *this is the first report of such a case*

CASE REPORT

A 30-year old Rh negative patient was first seen in our department in her sixth pregnancy Her first pregnancy in 1968 was terminated by artificial abortion Her second pregnancy in 1971 ended in a premature delivery after 34 weeks of an infant weighing 2 000 g the newborn developed severe HDN and died after one week Her third pregnancy in 1972 terminated in early spontaneous abortion Her fourth pregnancy in 1973 ended in a premature delivery at 28 weeks gestation of a fetus weighing 1 100 g which died shortly after delivery At 27 weeks of this gestation the Coombs test was positive 1 1'8 Her fifth pregnancy in 1974 was terminated by artificial abortion No anti D was administered after any pregnancy

When seen in our department in 1976 the woman was 12 weeks into her sixth pregnancy On ultrasonographic examination a twin pregnancy was diagnosed and because of an already known cervical incompetence a cerclage was performed At 14 weeks gestation the Coombs test was positive 1 2 it rose gradually to 1 32 at 20 weeks then unexpectedly it dropped to 1 4 Similar values were obtained by repeated measurements and different laboratories Ultrasonographic examinations performed at 17 and 20 weeks of gestation demonstrated no pathological findings At 28 weeks gestation there was ultrasonographic evidence of polyhydramnios large placenta and most prominent ascites in both fetuses (Fig 1–4) The patient went into labour spontaneously in the

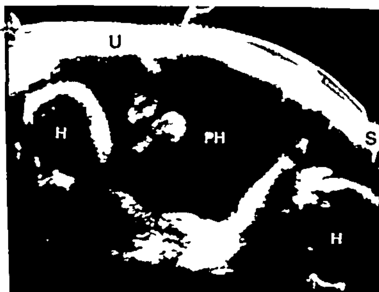


Fig 1 At 28 weeks gestation mild oblique cross section shows both heads and polyhydramnios *U* umbilicus *H* heads *S* symphysis *PH* polyhydramnios



Fig 2 Transverse cross section showing anterior hydropic placenta polyhydramnios and both fetuses *AW* abdominal wall *PL* placenta

9th week of gestation and delivered hydropic twins weighing 950 and 1100 g Neonatal death occurred immediately after delivery

DISCUSSION

Despite large scale anti D administration the Rh isoimmunisation still presents a problem in obstetrics Diagnostic procedures in patients whose fetuses are jeopardized by Rh isoimmunisation processes namely repeated amniocenteses for amniotic fluid bilirubin assessments are associated with some risks (4) Various reports suggest that careful ultrasonographic surveillance may find a intrauterine fetal demise in pregnancies complicated by Rh isoimmunisation

It has been demonstrated that placental hydrops (3 5) is the first ultrasonographic sign of isoimmunisation followed by hydrops foetalis d



Fig 3 Transverse cross section—ascites in both fetuses *AW* abdominal wall *AF* amniotic fluid *a* ascites



Fig 4 Transverse scan of one of the fetuses showing fetal abdomen which has a perfectly circular shape filled with ascites The intestines are concentrated in the center forming a homogeneous round mass *a* ascites *i* intestines *AF* amniotic fluid

contour of the head and chest fetal hepato- and cardiomegaly (1 5) In a few cases fetal ascites could be diagnosed by ultrasonography (2 5)

These findings on the dynamics of fetal involvement in the isoimmunisation process may facilitate handling of such pregnancies and indicate the proper timing for intervention In our case we must point out that the patient disappeared from ultrasonographic surveillance after the 20th week of gestation because of the recurrent low Coombs test titers She was readmitted by her physician in the 8th week because of suspected polyhydramnios ultrasonographic examination at this time revealed the severity of the condition of both fetuses and the hopelessness of the case

Amniotic fluid volume estimation still presents a diagnostic problem on ultrasonographic examination and in fact until now is based on the empirical experience of the examiner Even if the exact amounts of amniotic fluid cannot be estimated a well trained ultrasonographer can easily diagnose polyhydramnios

Hydropic placenta on the other hand can be very well defined by ultrasound and precisely measured by calipers on the A scan system The typical snow flake like appearance of a hydropic placenta on B scan display can be obtained easily by proper attenuation of the transmitter The finding of this kind of placenta on a routine ultrasonographic examination marks the beginning of a search for the causative conditions which can be diabetes or Rh isoimmunisation

Fetal ascites is a rare finding on ultrasonographic examination and very few articles have appeared in the obstetric ultrasonographic literature This condition presents such a specific picture on ultrasonography that it is nearly impossible to miss The fetal abdomen has a perfectly circular shape filled with fluid and the intestines are concentrated in the center forming a homogeneous round mass In our case there were no other pathological findings as have been described by others (1 5)

We present this case because of the antenatal diagnosis of fetal ascites in a twin pregnancy by B scan technique which to the best of our knowledge has not been previously reported

REFERENCES

1 Campogrande M Brugnoli C A & Mattone P G Impiego degli ultrasuoni nella diagnostica della isoimmunizzazione anti Rh Minerva Ginecol *26* 571 1974

2 Cederqvist L L Williams L R & Symchych P S Prenatal diagnosis of fetal ascites by ultrasound Am J Obstet Gynecol *128* 229 1977

3 Hollander H J & Mast H Intrauterine Dickenmessung der Placenta mittels Ultraschalls bei normalen Schwangerschaften und bei Rhesus Inkompatibilitat Geburtshilfe Frauenheilkd *28* 626 1968

4 Scrimgeour J B Amniocentesis Technique and Complications Antenatal Diagnosis of Genetic Diseases (ed A E H Emery) pp 11-39 Williams & Wilkins Baltimore 1973
5 Weib P A M Typische Ultraschallbilder bei schwerer foetaler Rhesus Erkrankung Geburtshilfe Frauenheilkd *34* 640 1974

Submitted for publication March 29 19 8

Zwi Weinraub M D
Dept of Obst and Gyn
Ultrasonographic Sub-Unit
Asaf Harofe Government Hospital
Zerifin Israel

Acta Obstet Gynecol Scand 58 221–223 1979

CASE REPORT

COLPOSCOPY IN A CASE OF SUSPECTED GENITAL HERPES INFECTION IN EARLY PREGNANCY

J M van Meir A C Drogendijk J W Wladimiroff
and G Wielenga

*From the Departments of Obstetrics and Gynaecology and Clinical Pathology
Erasmus University Rotterdam The Netherlands*

A pregnant patient with suspected genital herpes infection was investigated by colposcopy cytology and virological examination Visual examinations of the uterine cervix may suggest malignant disease when histological and virological examination show herpes virus infection The colposcopic appearance of genital herpes of the cervix is presented

CASE REPORT

A 3? year old primigravida of 12 weeks gestation visited the outpatient department complaining of recent vaginal discharge vulval irritation and itching The vulva appeared slightly inflamed An area around the external os had a macroscopically suspicious appearance and bled on contact Uterine size was equivalent to 12 weeks gestation Adnexa and parametria felt normal

Colposcopy was performed The cervix was cleansed with a 0 9% saline solution (2) The lesion had an irregular [illegible]ce with thin vesicles and some small craters In contrast to ordinary retention cysts these vesicles contained clear watery fluid (Fig 1) Using a green filter the capillary pattern appeared to be atypical there was a wide variation in vessel configuration and some of the capillaries were staple shaped or cork screw shaped

Application of Lugol s iodine solution revealed a sharply demarcated non staining area around the external os with an extension into the anterior fornix The vascular pattern of this latter area resembled that of a coarse mosaic pattern The colposcopic diagnosis was invasive cancer

The results of the cervical smear and three punch biopsies taken of the suspicious area were rather surprising The cervical smear revealed multinucleate giant cells with inclusion bodies inside the hazy nuclei which as a rule are characteristic for genital herpes infection Fig ? (3) There were no signs of malignancy Histology of the punch biopsies showed acute necrotising cervicitis and the same giant cells with inclusion bodies as observed in the cervical smear Fig 3

Some cervical epithelium was taken for virological examination but electron microscopic examination and isolation in a tissue culture cell line showed negative results It should be mentioned however that by the time virus studies were made the abnormal pattern observed during the first colposcopic examination had disappeared The colposcopic picture now resembled that of an old transformation zone A second cervical smear test was entirely normal

Complement fixing serum antibodies to Herpes simplex type II were 1 8 at the time and 1 16 three weeks later

DISCUSSION

This was almost certainly a case of genital herpes infection although the actual presence of the virus was never proven This was probably due to late culturing of cervical material as a result of the initial macroscopic and colposcopic diagnosis of invasive carcinoma

However in retrospect the clinical features certainly pointed at herpes infection More substantial evidence was obtained from cytological and histological investigation The presence of multinucleate giant cells with inclusion bodies inside hazy nuclei is almost typical of the presence of herpes infection

Jordan & Singer described a colposcopic picture of general necrosis and atypical vascularization in case of proven genital herpes infection which very much resembles the colposcopic findings in the case presented in this paper (1) It therefore seems to be desirable to bear in mind the possibility of herpes infection when such lesions are colposcopically encountered Isolation of herpes virus should then be attempted in order to reach an accurate diagnosis

ANNOUNCEMENT

IX Meeting of the International Study Group for Steroid Hormones will be held in Rome December 1979

Topics

Endocrinological cancer

breast cancer

prostate cancer

Ovarian function and disease

Further information may be obtained from

Professor Carlo Conti

International Study Group for Steroid Hormones

Clinica Medica V Policlinico Umberto I Università di Roma

Roma

Italy

International Symposium on the Menopause and the P[illegible] Menopause will be arranged in Rome Italy June 2, [illegible] 1979

Topics

- New metabol[illegible] findings on estrogens and pro[illegible] in relation to coagulation and osteoporosis
- New concepts on estrogen receptor [illegible] human data in relation to E1 E2 E3 and [illegible] trogens
- Effect of estrogen on catecholamine levels in the pre-[illegible] post menopausal woman and its effect on [illegible] the menopause
- Calcium metabolism and the clinical aspects of [illegible] treatment of osteoporosis with estrogens

  Effect of hormone replacement therapy on glucose t[illegible] ance clotting factors fibrinolysis and platelet behavi[illegible] post menopausal women and other clinical observa[illegible]
- Effect of estrogen and progestogen on the endom[illegible] and breast tissue in the postmenopausal woman

Acta Obstet Gynecol Scand 58 225–229 1979

AMNIOTIC FLUID PHOSPHATIDYLINOSITOL AND PHOSPHATIDYLGLYCEROL

I Normal pregnancies

J Skjæraasen and S Stray Pedersen

From the Department of Obstetrics and Gynecology Rikshospitalet University of Oslo Oslo Norway

Abstract Phosphatidylinositol (PI) and phosphatidylglycerol (PG) appear normally in the amniotic fluid during the last weeks of pregnancy The present study indicated as have previous studies (5 6 8 10) that these phospholipids are linked to the surfactant system in the fetal lung

The concentrations of lecithin (L) PI PG and sphingomyelin (S) were measured in 207 samples from 165 normal pregnancies The augmentation in PI was found to parallel that in lecithin and the PI/S ratios reached maximum values at about 36 weeks of gestation The augmentation in PG appeared about two weeks later

Eleven premature infants who contracted respiratory distress syndrome (RDS) had significantly lower PG concentrations than 15 premature infants with no RDS ($p<0.01$) No correlation to the PI concentrations could be observed All but one of the 11 affected infants had low L/S ratios

The surfactant system and the amniotic fluid may contain a wide variety of different phospholipids of which the quantitatively most important ones are lecithin (L) phosphatidylethanolamine sphingomyelin (S) phosphatidylserine phosphatidylinositol (PI) and phosphatidylglycerol (PG) (1 8) Studies of amniotic fluid phospholipids have predominantly been concentrated upon lecithin which obviously represents the main factor of the surfactant system in the fetal lung

Development of RDS in the neonates has been observed in cases in which the amniotic fluid has shown sufficient amounts of lecithin (2 3 4 9) During the last few years therefore special interest has been focused on other phospholipids in the amniotic fluid in particular PI and PG and their eventual role as constituents of the surfactant (5 6 8 10)

In the present investigation PI and PG have been measured in the amniotic fluid from women with normal pregnancies The aim of the study was to obtain informations concerning the content of these phospholipids at *different gestational stages during the* last trimester and to elucidate their role in the prevention of RDS in the newborn infant

MATERIAL AND METHODS

Patients and sample collections 207 samples of amniotic fluid were collected from 165 women who were admitted to the Department of Obstetrics and Gynecology Rikshospitalet University of Oslo The patients included represented earlier Rhesus immunized women with a Rhesus negative baby in the actual pregnancy or no pathological hemolysis (Liley Zone I) and women with normal pregnancies The 207 amniotic fluid specimens were drawn at different intervals after 28th weeks of gestation

The collections were performed by transabdominal amniocentesis transuterine puncture at cesarean sections or by puncture of the amniotic sac during vaginal deliveries Samples grossly contaminated with blood or meconium were discarded The amniotic fluid were centrifugated and usually immediately examined Some samples were kept frozen at -20 C and analyzed after thawing for about one hour at room temperature

Tracheal fluid was collected from three newborns delivered by cesarean section Immediately after the delivery they were intubated and aspirated The results of the phospholipid analyses in tracheal fluid were compared to those measured in the amniotic fluid sample obtained by transuterine puncture

The phospholipid composition of the last amniotic fluid sample was related to the clinical outcome with respect to RDS in the infant In 48 of the 165 infants the samples were collected more than 1 week prior to the delivery and were considered unreliable for this purpose

The criteria used for the diagnosis of RDS were similar to those employed in earlier investigations (7)

Gestational age has in the text been given in weeks meaning completed weeks (i e 39 weeks = 273 279 days)

Phospholipid analyses

Extraction and separation of the phospholipids The amniotic fluid was centrifugated at 1 050 g in 5 minutes The extraction was performed by methanol/chloroform followed by evaporation of the chloroform phase under N_2 and cold acetone precipitation

Separation was performed by thin layer chromatography on silica gel with 5 per cent ammonium sulphate In order to ensure optimal separation of the phospholipids under study a series of preliminary experiments was carried out using fluid media of different composition In one-dimensional chromatography best separation was obtained by the use of a medium containing chloroform methanol conc acetic acid H_2O (50:25:7:3 by volume) When the two-dimensional method was employed the plates were run for 30

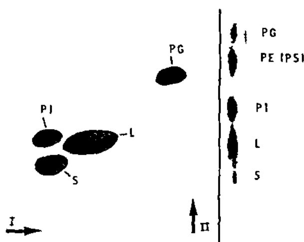


Fig 1 Left side two dimensional chromatogram (drawing) The arrows show the direction of the first (I) and second (II) run Right side One dimensional chromatogram (photography)
L = lecithin PE = phosphatidylethanolamine PS = phosphatidylserine PI = phosphatidylinositol PG = phosphatidylglycerol S = sphingomyelin

minutes in chloroform methanol NH OH (conc) H_2O (130 60 5 4) dried at 70 C for 5 minutes and then turned 90 and run in a new medium containing chloroform methanol conc acetic acid H_2O (160 50 12 4) for about 30 minutes

The typical distribution of the phospholipid spots on the dimensional and the two-dimensional chromatograms illustrated in Fig 1

tification of PI and PG The identification of I I and spots on the chromatograms was attempted in a preliminary study by qualitative chemical procedures and by co chromatography of phospholipid standards About 15 different methods predominantly spraying tests were employed in order to obtain a chemical characterization of the spots (i e tests for free amino and hydroxyl groups choline sugars reducing or oxidating substances alcohols etc) (12) Following chemicals were used as standards Lecithin PI PG Sphingomyeline Phosphatidylethanolamine Phosphatidyl L serine Phosphatidyl dimethyl ethanolamine Lysophosphatidylethanolamine Dilineoyl L α lecithin L 3 phosphatidyl N N dimethylethanolamine The chemicals were purchased from Supelco Sigma and Koch Light Laboratories Ltd

Measurements of lipid phosphorus were performed on 84 of the samples of amniotic fluid The spots were visualized by iodine vapour scraped off and digested for one hour at 190 C with 0 4 ml concentrated perchloric acid The phosphorus content was read photometrically at 830 mμ after addition of ammonium molybdate ascorbic acid and H_2O according to the method described by Lindback *et al* (7)

Densitometrical measurements of the lipids were performed on one-dimensional chromatograms of 123 of the samples after charring of the plates and using a Joyce Chromoscan In 25 of these samples satisfactory separation of I G was not achieved and did not allow a reliable estimation of this phospholipid

The concentrations of lecithin PI and PG were related to that of sphingomyelin and presented as ratios in order to eliminate variations due to differences in amniotic fluid volume *The densitometrically determined ratios* were smaller representing on an average about one third of the corresponding ratios determined chemically Consequently then, a densitometrically determined L/S ratio = 2 corresponded to a chemically determined ratio of about 5-6 Densitometrically estimated L/S ratios ≤ 1 5 were according to previous studies (11) named immature signalling a high *risk of RDS in normal pregnancies L/S ratios* = 1 6-1 9 were named intermediate indicating minor risk of RDS
Calculation of statistical significance was performed by the use of the Wilcoxon two-sided test and the rank correlation test (Kendall) Statistical estimations were employed only on chemically measured data

RESULTS

The median values for the L/S PI/S and PG/S ratios obtained in the different samples of amniotic fluid are shown in Fig 2 As expected the ratios determined chemically (measurements of lipid phos-

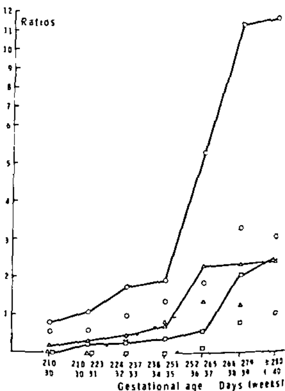


Fig 2 Median values of phospholipid ratios obtained in 207 samples of amniotic fluid from 165 normal pregnancies
○ L/S ratio △ PI/S ratio □ PG/S ratio
— chemical analyses — densitometrical analyses

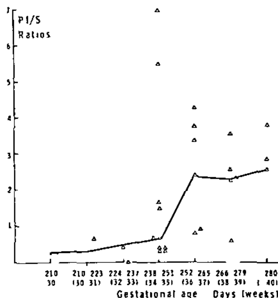


Fig 3 Chemically determined PI/S ratios (△) in 84 samples of amniotic fluid from normal pregnancies —— median values

phorus) were found to be about three times as high as the corresponding ratios determined densitometrical ly The mutual relationship between the phospholipid ratios however appeared to be identical with the two methods The L/S ratio followed the characteristical pattern showing the typical increase from 34-36 weeks of pregnancy The L/S ratios showed great individual variations as were also observed for the PI/S and PG/S ratios (Figs 3 and 4)

An intimate relationship was observed between the oncentrations of lecithin and PI (Fig 2) Up to a bout 36th week of gestation PI followed lecithin very closely giving a Kendall correlation coefficient of 0 69 which was highly significant (p<0 0001) PI appeared to reach maximum concentrations represent ing about 40 per cent of the lecithin concentration at 36th 37th week of gestation and then remained fairly constant

On the other hand the augmentation in PG did not seem to be related to that of lecithin or PI (Fig 2) Prior to a gestational age of 34 weeks PG could not be detected in the amniotic fluid by the densitometri cal method and the phosphorus measurements re vealed only trace amounts of this phospholipid After the 36th week PG increased markedly reaching maxi mum levels between 38th and 40th week of gestation (10-15 per cent of the lecithin concentration)

None of the babies delivered ≥266 days of gesta tion except for one case developed RDS Lack of PG was recorded in two of the non affected infants The ratios obtained by phosphorus analyses in 26 in fants delivered <266 days of gestation are presented in Fig 5 in which the RDS cases are marked with fil led symbols The densitometrically measured ratios for the exceptional case with RDS (delivered >294 days birthweight 3 500 g) are also included in the fig ure All samples were collected within one week prior to delivery the majority during delivery Eleven of the 26 neonates delivered <266 days contracted RDS

As may be observed from Fig 5 the L/S ratios in eight of the 11 RDS infants were immature and in two cases intermediate (see Methods) The single exceptional case in which RDS developed in the neonate in spite of a highly mature L/S ratio represented a gra vida 2 who was under observation for prediabetes which was not confirmed

No association seemed to exist between the differ ent PI/S ratios and the occurrence of RDS (Fig 5) On the contrary a rather close relationship was observed between the concentration of PG and the risk of RDS The concentrations of PG in the amniotic fluid from the RDS cases were found to be signifi cantly (p<0 01) lower than those measured in the non affected cases (Fig 5) In 8 of the 11 infants with RDS PG was either unmeasurable or present in an ex tremely low concentration The PG/S ratios among

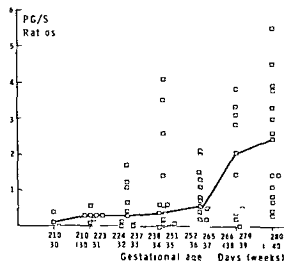


Fig 4 Chemically determined PG/S ratios (□) in 84 sam ples of amniotic fluid from normal pregnancies —— medi an values

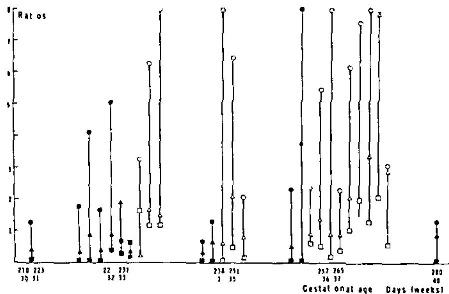


Fig 5 The individual phospholipid ratios chemically determined from 26 infants born < 266 days and the densitometrical ratios from one infant born > 280 days of gestation
○ L/S △ PI/S □ PG/S ratios in the individual samples Filled symbols infants with RDS

the non affected infants born at 32 33 weeks were substantially higher than the median values quoted in Fig 4 but only one of these infants had an immature L/S ratio

In Table I the individual results obtained in the tracheal fluid from the three infants have been compared to those obtained in the amniotic fluid The concentrations of lecithin PI and PG were considera ly higher in the tracheal fluid whereas the mutual tionship between the concentrations of these pholipids resembled that of the amniotic fluid

n pregnancies in which the phospholipid ratios were determined densitometrically three of nine infants born <266 days developed RDS PG was lacking in all three cases and the L/S ratio were immature

DISCUSSION

The content and the composition of phospholipids in the amniotic fluid may reflect the maturation of very different organs or structures in the fetus (1) There seems to be a general agreement that the surfactant system represents the major source of amniotic fluid lecithin PI and PG (5 6 8 10) The results obtained by analyses of the tracheal fluid collected immediately post partum (Table I) represent a line of evidence to this hypothesis since all three phospholipids were found to be present in the tracheal fluid in concentrations which exceeded those of the amniotic fluid

As shown in Figs 2 and 3 the augmentation in PI in the amniotic fluid appeared to be intimately correlated with that of lecithin (p<0 0001) suggesting either common precursors and/or the same enzymatic induction for the biosynthesis of these phospholipids in the fetal lung The content of PI reached a maximum at 36th week of gestation representing about 40 per cent of the lecithin content After this stage the concentration of PI remained unchanged

The values obtained for the concentrations of PG indicated the synthesis of this phospholipid to be independent of that of lecithin and PI The increase in the content of PG took place at 38 39 weeks of gestation and maximum levels were achieved at term representing about 15 20 per cent of the lecithin concentration These findings are in agreement with those reported by Hallman *et al* (5)

Surface activity represents a characteristical physical property of many phospholipids Measurements using a Wilhelmy balance have shown that PI has a low surface activity whereas lecithin and PG both are highly surface active substances (5 8) There is no

Table I *Concentrations of lecithin (L) phosphatidyl inositol (PI) and phosphatidylglycerol (PG) in tracheal fluid as compared to those in amniotic fluid*

Patients	Gest age days	L_{trach}/L_{amn}	PI_{trach}/PI_{amn}	PG_{trach}/PG_{amn}
No 1	274	2 4	3 5	1 5
No 2	288	4 4	2 5	8 9
No 3	295	19 9	20 0	17 9

doubt however that most of the activity of the surfactant must be ascribed to lecithin since it represents quantitatively the most important component This does not preclude other phospholipids such as PI and PG being of great importance since these substances may stabilize and maintain the structural integrity of the protein lipid complexes in the surfactant

The results presented in Fig 5 offer great support to the accepted notion that in normal pregnancies there is practically no risk of RDS if the amniotic fluid shows ample lecithin concentrations Only one of the 11 cases with RDS had a mature L/S ratio (prediabetes in the mother?) the remaining ten RDS infants had intermediate or immature L/S ratios No association could be observed between the amniotic fluid content of PI and the incidence of RDS High PI/S ratios did not appear to represent a protection against RDS and this observation correlates well with the fact mentioned above that PI has a low surface activity The possibility exists that the disease might be less severe in infants showing high PI concentration since the presence of PI nevertheless reflects a certain level of production of surfactant

PG/S ratios were found to be significantly lower in cases with RDS as compared to those in the non affected infants ($p<0.01$) In the majority of the infants with RDS PG was either unmeasurable or detectable only in trace concentrations Admittedly very low concentrations of PG were also observed in several cases in which RDS did not occur Abscence of PG at birth however does not necessarily indicate that RDS may be inevitable since the synthesis of PG may be activated during the first neonatal hours (6)

In conclusion PG seems to be of great significance for the prevention of RDS in the neonate In normal pregnancies analyses of the surfactant system by means of the L/S ratio are usually sufficient for the assessment of pulmonary functional maturity However as indicated by the present investigation measurements of PG may in this respect give additional and valuable informations The detection of high concentrations of PG e g in cases with intermediate or immature L/S ratios may indicate a reduced risk of RDS

ACKNOWLEDGEMENTS

We wish to thank Professor K Bjøro and Assistant Professor Narve Moe Department of Gynecology and Obstetrics Rikshospitalet Oslo for valuable help and assitance

REFERENCES

1 Ansell G B Hawthorne J N & Dawson R M C Form and function of phospholipids Elsevier Scientific Publishing Company Ed 2 Amsterdam 1973
2 Cruz A C Buhi W C Birk S A & Spellacy W N Respiratory distress syndrome with mature lecithin/sphingomyelin ratios Diabetes mellitus and low Apgar score Am J Obstet Gynecol *126* 78 1976
3 Farell P M Indices of fetal maturation in diabetic pregnancies Lancet *I* 596 1976
4 Gabbe S G Lowensohn R I Mestman J H Freeman R K & Goebelsmann U Lecithin/sphingomyelin ratio in pregnancies complicated by diabetes mellitus Am J Obstet Gynecol *128* 757 1977
5 Hallman M Kulovich M Kirkpatrick E Sugarman M G & Gluck L Phosphatidylinositol and phosphatidylglycerol in amniotic fluid Indices of lung maturity Am J Obstet Gynecol *125* 613 1976
6 Hallman M Feldman B H Kirkpatrick E & Gluck L Absence of phosphatidylglycerol (PG) in respiratory distress syndrome in the newborn Study of the minor surfactant phospholipids in newborns Pediatr Res *11* 714 1977
7 Lindback T Frantz T Skjæraasen J & Graven S Phospholipids in amniotic fluid Acta Obstet Gynecol Scand *53* 219 1974
8 Rooney S A Canavan P M & Motoyama E K The identification of phosphatidylglycerol in the rat rabbit monkey and human lung Biochem Biophys Acta *360* 56 1974
9 Skjæraasen J & Lindback T Phospholipid concentrations in amniotic fluid from diabetic pregnant women Acta Obstet Gynecol Scand *55* 225 1976
10 Skjæraasen J & Stray Pedersen S Phosphatidylinositol and phosphatidylglycerol in amniotic fluid in normal and diabetic women *In* Abstract 6th Nordic Congress in Perinatal Medicine Oulu Sept 1977
11 Skjæraasen J Amniotic fluid phospholipid concentrations in pregnancies with preeclampsia and/or intrauterine growth retardation of the fetus Acta Obstet Gynecol Scand *58* 191 1979
12 Stahl E Dunnschicht Chromatographie Ein Laboratorium Handbuch 2nd Edition Springer Verlag 1967

Submitted for publication August 4 1978

J Skjæraasen M D
Department of Obstetrics and Gynecology
Rikshospitalet
Oslo 5
Norway

Acta Obstet Gynecol Scand 58 231 – 233 1979

SERUM BETA HUMAN CHORIONIC GONADOTROPHIN LEVELS IN THE EARLY DIAGNOSIS OF ECTOPIC PREGNANCY

Viveca Lundström Katarina Bremme Peter Eneroth
Inga Nygård and Margareta Sundvall

From the Department of Obstetrics and Gynecology Karolinska Hospital Stockholm Sweden

Abstract Beta HCG in serum was anal sed in 64 cases of ectopic tubal pregnancy who were operated upon during 1974 – 1976 The case material was divided into three different groups ruptured ectopic pregnancy ectopic pregnancy accompanied by amenorrhea or adnexal mass and ectopic pregnancy without palpable adnexal mass and amenorrhea The mean HCG levels for the three groups were 8 790 IU/l 2 580 IU/l and 690 IU/l respectively which related more to the symptoms than to the estimated length of pregnancy Eleven per cent of the women had an IUD and five per cent were taking low dose gestagens Screening of cases with acute lower abdominal pain or irregular vaginal bleeding with beta HCG in serum will facilitate an early diagnosis of ectopic pregnancy and be of special value in patients with less typical symptoms

The immunological test based on inhibition of agglutination by urinary HCG with a sensitivity of approximately 1 000 – 1 500 IU/l has been reported to give positive results in only 50 to 80 per cent of the patients with ectopic pregnancy (3 5) The use of specific highly sensitive methods for the measurement of HCG in serum has been suggested to facilitate the early diagnosis of ectopic pregnancy Thus Saxena (11) recently reported on the use of radioreceptor assay of HCG in serum as a diagnostic aid in cases of suspected ectopic pregnancy This method has the advantage of combining a high sensitivity with a rapid analysis approximately one hour The author claims that a negative HCG test excludes an ectopic pregnancy

Radioimmunoassay of the beta subunit of HCG in serum offers an alternative method for determination of chorionic gonadotrophin with a combination of specificity for HCG and high sensitivity (6) It is an obvious advantage that cross reaction with LH can be avoided This is especially important in the differentiation between ovulatory bleeding and ectopic pregnancy

The following study was undertaken to evaluate the accuracy of routine serum beta HCG measurements in the diagnosis of ectopic pregnancy

PATIENTS AND METHODS

The study comprised 83 patients with ectopic tubal pregnancy operated upon at the Karolinska Hospital during the period 1974 October 1976 In 64 cases one or more blood samples were analysed for HCG The occurrence of amenorrhea and an adnexal mass as well as the number of patients treated for salpingitis before the correct diagnosis was made are summarized in Table I The percentage of ruptured tubal pregnancies and the use of contraceptive agents in the patients studied is presented in Table II

The 64 cases in whom HCG was determined have been divided into three different groups according to the history (amenorrhea pain and irregular bleeding) and according to the clinical signs (tenderness and mass) as shown in Table III

HCG was determined in serum using a commercial kit (Hypolab S A Coinsins Switzerland) calibrated against the 2nd international standard The time taken for this determination was 36 hours These samples were later reanalyzed using a kit (Hypolab) for beta HCG which has been in routine use since June 1976 This analysis can be completed in eight hours At least 6 IU/l serum could be detected Intra assay variation was below 10 per cent Each sample was analyzed in duplicate in at least three concentrations of serum (undiluted 1 25 1 50)

RESULTS

From Table I it is evident that clinical findings are not reliable for making the diagnosis of tubal pregnancy Amenorrhea was present in only 50 per cent and a palpable mass in only 54 per cent of the patients Neither amenorrhea nor a palpable mass was observed in 13 cases (16 per cent) The diagnostic difficulties are further illustrated by the fact that eleven per cent of the patients had an IUD and 5 per cent were taking daily low dose gestagen tablets (Table II) Furthermore in 20 out of 83 cases (24 per cent) treatment for

Table I *History and clinical observations in patients with ectopic pregnancies operated upon during 1974 until October 1976*

Year	Number	Amenorrhea	Adnexal mass	First diagn salpingitis	HCG analysed
1974	33	15	22	9	24
1975	15	12	10	1	7
1976	35	15	12	10	33
Total	83	42	44	20	64

salpingitis was given before the correct diagnosis was made

In all the 64 patients with a tubal pregnancy HCG could be detected in plasma by the beta HCG method The majority of the patients 59 out of 64 had a concentration of HCG below 10 000 IU/l which in most patients is a subnormal value if correlated to the estimated length of gestation (Table III) However in four patients with rupture of the fallopian tube and in one patient with a tubal abortion serum beta HCG levels in close accordance with the estimated length of gestation was found During the years this study was in progress low HCG values were taken into consideration to justify laparascopy in 5 cases where an intrauterine pregnancy was [illegible]blished The number of HCG analyses carried [illegible] vague or strong suspicion of extrauterine [illegible] was high and increased over the years [illegible]g a total of 1 600 in 1976 and by May 1977 at [illegible] seven patients with ectopic pregnancies had serum beta HCG levels above 20 000 IU/l

It was considered of interest to calculate the mean values of HCG separately for the three different groups of ectopic pregnancy according to symptoms and correlated these to the interval after the estimated last menstrual period These data are presented in Fig 1 and Table III The mean level for normal pregnancy was calculated in 100 cases admitted to the hospital for legal termination of an apparently normal pregnancy Of particular interest are the patients in group I where clinical signs gave very little support for the correct diagnosis The low values aided in a presumptive early diagnosis of ectopic pregnancy before prolonged amenorrhea and/or tubal mass appeared

This early diagnosis might be one explanation for the decrease in percentage of ruptured ectopic pregnancies found after the introduction of routine serum beta HCG determination The incidence of tubal rupture thus decreased from 48 per cent to 14 per cent of tubal ectopic pregnancies during the study In those women having an IUD only one case of tubal rupture occurred In another 14 cases of extrauterine pregnancies recorded during the first six months during 1977 four patients had an IUD without a ruptured fallopian tube Thus the incidence of ruptured fallopian tube in this group of patients was one out of 14 which should be compared with 18 out of 78 among the amalgamated patients

DISCUSSION

Culdocentesis has earlier been the most common diagnostic procedure used in cases of ectopic pregnancy (1) but many authors have lately recommended laparascopy as the safest instrumental aid for the accurate early diagnosis of ectopic pregnancy Samuelsson (10) reported 489 laparascopies performed on the suspicion of ectopic pregnancy The diagnosis was verified in 37 per cent a normal intrauterine pregnancy was found in 19 per cent and normal gynecological findings in 24 per cent of the patients These figures should be kept in mind when considering that this operation carries a risk even if complications are rare in the hands of experienced surgeons The ultrasound technique can be used for confirmation of an ectopic pregnancy (12) however an intrauterine pregnancy cannot be identified with this technique at present until the 7 8th week It is an established fact that urinary HCG levels are lowered in ectopic pregnancy (2 8 13) even if methods less sensitive than RIA are employed Winter and Weiss (12) investigated 244 patients with ectopic pregnancies and found reduced mean HCG levels in 20±13 per cent whereas eleven per cent had normal values It is however an advantage to be able to only have to

Table II *Case material operated for ectopic pregnancy during 1974 until October 1976*

Year	Number	Rupture %	Users of contraceptive agents IUD	low dose gestagen
1974	33	48	1	1
1975	15	37	0	2
1976	35	14	8	1
Total	83	31	9	4

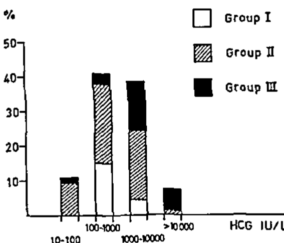


Fig 1 Percentage of ectopic pregnancies in different groups correlated with the range of serum HCG concentration
Group I Atypical ectopic pregnancy (No amenorrhea no adnexal mass)
Group II Tubal abortion with typical history
Group III Tubal rupture

draw blood in emergency situations especially when a method specific for the β subunit of HCG is subsequently applied As reported in this paper serum beta HCG could be detected in all patients in whom ectopic pregnancy was verifi d at operation It is obvious that in patients with the clinical signs of an ectopic pregnancy there is no need to delay the treatment by waiting for a quantitative estimation of serum beta HCG In these cases laparascopy and/or laparatomy is the method of choice Ectopic pregnancy associated with an IUD offers a particular diagnostic problem as pointed out recently by Hallat (4) The same diagnostic difficulties are also present in patients on daily low dose gestagen treatment (9)

In the less typical cases (group I) a routine estimation of serum HCG will facilitate the early diagnosis of ectopic pregnancy A low HCG value will suggest a pathological pregnancy Repeated clinical examination or ultrasound will differentiate between tubal pregnancy and missed abortion It must be strongly emphasized that a normal HCG value does not exclude an ectopic pregnancy whereas a negative beta HCG in our experience excludes an ectopic pregnancy as also reported by Milwidsky *et al* (7) The percentage of ruptured tubal pregnancies decreased from 48 per cent to 14 per cent during the three years of this study and only one of these was associated with an IUD Although the total number of women with IUDs was relatively small in our study group it appears that tubal rupture occurred less frequently

It is possible that the routine analysis of serum beta HCG in patients with atypical gynecological symptoms will result in a higher percentage of ectopic pregnancies being recognized The frequency of ectopic pregnancy has increased from 1 15 per cent in 1973 to 1 94 per cent of all pregnancies in our hospital but whether this increase is due to improved diagnostic methods or to other reasons is unclear Probably some cases of complete spontaneous tubal abortion who would otherwise have gone undiagnosed will now be detected Thus in one patient symptoms had completely disappeared when she was seen one week after the first visit During this time the serum had HCG decreased from 150 IU/l to 15 IU/l This patient was not operated upon but had possibly experienced a complete tubal abortion Whether early diagnosis and the possibility of a more conservative surgical approach will result in less damage both to the fallopian tube and also to subsequent fertility cannot yet be evaluated

Table III *Serum levels of HCG±S D for different groups of patients with verified ectopic pregnancy*

Group	Number	Mean HCG IU/l±S D	Range IU/l	Estimated range of pregnancy length	OC	IUD
I No amenorrhoea No palpable adnexal mass	13	670±443 (28 000±19 000)†	100– 1 100	5– 8	0	3
II Amenorrhea or palpable adnexal mass	35	580+15 760 (51 700±32 000)†	56–47 000	5–10	3	5
III Ruptured ectopic pregnancy	16	8 790±10 760 (50 400±19 600)†	105–40 000	6–10	1	1

† Figures within parentheses denote mean values obtained in patients seeking therapeutic abortion

ACKNOWLEDGEMENTS

The authors are indebted to Associate Professor M Bygdeman for valuable suggestions and a critical review of the manuscript and to Ms L M Lindeholm for skilful typing of the manuscript

REFERENCES

1 Breen J L A 21 year old survey of 654 ectopic pregnancies Am J Obstet Gynecol *106* 1004 1970
2 Brody S Carlström G Human chorionic gonadotrophin in abnormal pregnancy Serum and urinary findings using various immunoassay techniques Acta Obstet Gynecol Scand *44* 32 1965
3 Glass R H Jesurun H M Immunologic pregnancy tests in ectopic pregnancy Obstet Gynecol *92* 23 1965
4 Hallat J G Ectopic pregnancy associated with the intrauterine device A study of seventy cases Am J Obstet Gynecol *15* 754 1976
5 Halpin T F Ectopic pregnancy The problem of diagnosis Am J Obstet Gynecol *106* 227 1970
6 Kosasa T S Taymor M L Goldstein D P & Levesque L A Use of radioimmunoassay specific for human chorionic gonadotrophin in the diagnosis of early ectopic pregnancy Obstet Gynecol Vol 42 *6* 868 1973
7 Milwidsky A Adoni A Palti Z Stark M & Segal S The significance of human chorionic gonadotrophin in blood serum for the early diagnosis of ectopic pregnancy Acta Obstet Gynecol Scand *56* 19 1977
8 Mishell D R Jr Davajan V Quantitative immunologic assay of human chorionic gonadotrophin in normal and abnormal pregnancy Am J Obstet Gynecol 96 231 1966
9 Rantakylä P Ylöstalo P Järvinen P A & Vuorjoki A Ectopic pregnancies and the use of intrauterine device and low dose progesterone contraception Acta Obstet Gynecol Scand *56* 61 1977
10 Samuelsson S Sjövall A Laparascopy in suspected ectopic pregnancy Acta Obstet Gynecol Scand *51* 31 1972
11 Saxena B B & Landesman R The use of radioreceptorassay of human chorionic gonadotrophin for the diagnosis and management of ectopic pregnancy Fertility and Sterility *26* 397 1975
12 Schlensker K H Ultraschalldiagnostik beim verdacht auf extrauterineschwangerschaft Arch Gynaekol *219* 552 1975
13 Wide L Immunoassay of human gonadotropins Specificity problems and clinical application Advances in Obstetrics and Gynecology Vol 1 56 1967
14 Winter R & Weiss P A M Die choriongonadotrophin ausschedigung bei extrauterinegravidität Geburtshilfe Frauenheilkd 35 880 883 1975

Submitted for publication November 14 1977

Viveca Lundström M D
Department of Obstetrics and Gynecology
Karolinska Hospital
S–104 01 Stockholm
Sweden

Acta Obstet Gynecol Scand 58 235–238 1979

EFFECTS OF BETAMETHASONE ON PLASMA LEVELS OF ESTRIOL CORTISOL AND HCS IN LATE PREGNANCY

Jan Martin Maltau Kjell Torgeir Stokke and Narve Moe

From the Departments of Obstetrics and Gynecology and Clinical Chemistry
Rikshospitalet Oslo Norway

Abstract The effect of a single dose of betamethasone on the maternal plasma concentration of estriol and cortisol was studied The concentration of estriol decreased rapidly A maximal suppression of about 70 per cent was seen after 6-24 hours A similar influence on the maternal plasma concentration of cortisol was observed HCS (human chorionic somatomammotropin) was not influenced by betamethasone These facts have to be taken into consideration after treatment wi h synthetic corticosteroids in high risk pregnancies

Synthetic corticosteroids have been used for some time for the prevention of respiratory distress syndrome Administration of corticosteroids is known to suppress the concentration of estriol and cortisol in maternal blood (3) whereas the concentration of human chorionic somatomammotropin (HCS) is unaffected (6 8) There is however scanty information as to how soon the fall in estriol and cortisol occurs Furthermore conflicting reports exist concerning the degree of suppression (3 5 6)

In this paper further investigations of the hormonal changes in maternal plasma following corticosteroid administration are presented

MATERIAL AND METHODS

Patients Eight hospitalized patients in the last trimester of pregnancy were studied Four patients were given betamethasone and four patients served as controls Except for one patient in the betamethasone group who received treatment to inhibit uterine contractions none of the patients received any drugs Clinical details are given in Table I All patients were informed of the purpose of the study all gave their consent

Blood samples Twelve mg of betamethasone (Celestone Chronodose[R]) was given by intramuscular injection at 8 a m Heparinized blood was drawn just prior to this and every second hour during the next 6 hours

Daily samples were then obtained at 8 a m on the following four days Plasma was frozen and stored at 20 C until analyzed In the control group blood samples were obtained at the same intervals as in the betamethasone group

Hormone analyses All samples were run in duplicate and the complete series of samples from one patient were analyzed in the same run The concentration of unconjugated estriol in plasma was determined by radioimmunoassay Our own antiserum directed against 6-keto-estriol 6-carboxymethoxime BSA was raised in rabbits No chromatographic purification of the diethyl ether extract was performed since cross reaction with other steroids was insignificant The coefficient of variation (CV) (between assays) for estriol analysis was 10 per cent Cortisol in plasma was analyzed by a double antibody radioimmunoassay technique with reagents purchased from Diagnostic Products Corporation U S A The CV of the

Table I *Clinical data on the 8 patients in the study*

Pat	Age	Gravida	Maternal diagnosis	Gestational age at examination	Gestational age at delivery	Mode of delivery	Apgar score (1 – 5 min)	Birth weight	Placental weight
Betamethasone group									
AK	33	III	Prematurity	[illegible]8	36	Spontaneous	9 – 9	3060	No record
MH	22	III	Rhesus incomp	36	39	Spontaneous	9 – 10	3450	550
MK	31	I	Transverse position	39	40	Caesarean sect	7 – 10	3630	650
BS	25	I	Vaginal bleeding	35	38	Spontaneous	9 – 10	2950	No record
Control group									
GG	28	I	Thrombosis	31	36	Spontaneous	6 – 8	3630	500
AH	28	II	Placenta previa	38	40	Caesarean sect	9 – 10	3500	750
SK	27	II	Breech presentation	39	40	Caesarean sect	9 – 9	3850	700
LK	25	I	Observation	37	42	Spontaneous	9 – 10	3470	550

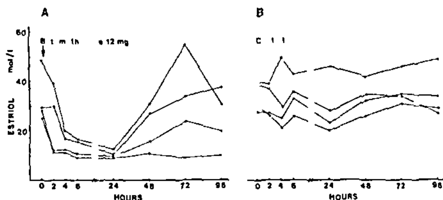


Fig 1 The concentration of unconjugated estriol in maternal plasma Four patients in each group A) after betamethasone 12 mg i m B) control group

analysis was 8 per cent *The plasma concentration of HCS* was determined by the HPL Immunoassay Kit supplied by the Radiochemical Centre Amersham England CV was 7 per cent

Statistical methods The Student s t test was used in the statistical analyses The mean percentage changes were calculated from the mean initial value

RESULTS

Estriol Fig 1 shows the concentration of unconjugated estriol in maternal plasma The initial level of striol did not differ significantly between the amethasone group and the control group Two rs after drug administration there was a moderate pression of estriol in the betamethasone group as compared with the initial value ($p < 0.10$) At 4 hours the estriol concentration had decreased to 46 per cent ($p < 0.05$) The lowest level 33 per cent of the initial value was observed 6-24 hours after the betamethasone load A precipitous increase took place in 3 of the patients on the second or third day whereas plasma estriol of one of the patients (M K) remained low throughout the study In the control group only small and irregular changes were seen

Cortisol Fig 2 shows the influence of betamethasone on the maternal plasma cortisol concentration After 2 hours there was a continuous decrease in the cortisol concentration The lowest level about 30 per cent of the initial value was reached after 24 to 48 hours Thereafter a gradual rise occurred reaching the initial value on the fourth day

HCS The concentration of HCS in the two groups was not influenced by a single dose of betamethasone Fig 3

DISCUSSION

Synthetic corticosteroids pass the placenta (1) and depress the ACTH release of the fetus (7) This leads to a reduced production of estriol precursors which in late pregnancy are mainly produced in the fetal adrenal glands (4) Our finding that estriol concentration in maternal plasma is reduced by about 50 per cent within 4 hours indicates a rapid transfer of betamethasone to the fetus This observation is in accordance with the work of Ballard *et al* (2) who detected glucocorticoid activity in cord blood one hour after the intramuscular administration of

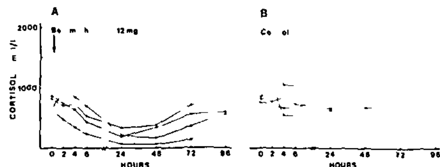


Fig 2 The concentration of cortisol in maternal plasma Four patients in each group A) after betamethasone 12 mg i m B) control group

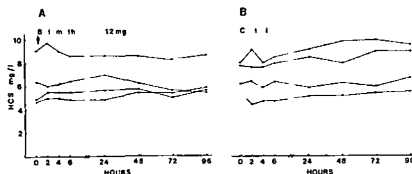


Fig 3 The concentration of HCS (human chorionic somatomammotropin) in maternal plasma Four patients in each group
A) after betamethasone 12 mg i m B) control group

betamethasone to the mother

Our study shows a maximal estriol suppression of about 70 per cent after 6-24 hours Kauppila *et al* (3) found the reduction to be about 20 per cent 24 hours after the start of treatment when 12 8 and 4 mg dexamethasone had been given intramuscularly on 3 consecutive days We cannot give any satisfactory explanation for this discrepancy Differences in the rate of placental transfer or different blocking effects on the fetal pituitary adrenal axis of the two agents might contribute to the different response In one of our patients the estriol concentration remained low throughout the study whereas in the others the initial level was reached on the third day

The reduction of maternal plasma cortisol was more gradual in onset than that of estriol The maximal fall in cortisol was nearly 70 per cent from the initial value This is in accordance with the findings of Liggins *et al* (5) and Ohrlander *et al* (6) They recorded a suppression of cortisol of about 70 and 85 per cent respectively 24 hours after 12 mg betamethasone i m Kauppila *et al* (3) found a suppression of about 50 per cent 24 hours after 12 mg dexamethasone intramuscularly In our study the cortisol concentration almost regained the initial level on the fourth day Ohrlander *et al* (6) found that when betamethasone was given on 3 consecutive days instead of one dose in our study the suppression lasted for 3 weeks

The concentration of HCS was completely unaffected by the betamethasone administration This finding is in agreement with the work of others (6 8)

In conclusion this study shows that administration of a single dose of betamethasone leads to a rapid and marked decrease in the concentration of estriol in maternal plasma This effect is probably due to placental transfer of the synthetic corticosteroid with subsequent suppression of fetal production of estriol precursors Betamethasone also influences maternal cortisol concentration A practical consequence of these findings is that when monitoring high risk pregnancies determination of estriol in maternal plasma will be misleading as a parameter of fetal well being for several days if betamethasone has been administered to the patient HCS on the other hand is produced by the placenta and is therefore not influenced by betamethasone

ACKNOWLEDGEMENTS

The technical assistance of Mrs Unni Færevaag is gratefully acknowledged

REFERENCES

1 Anderson A B Gennser G Jeremy J Y Ohrlander S Sayers L & Turnbull A C Placental transfer and metabolism of betamethasone in human pregnancy Obstet Gynecol *49* 471 1977
2 Ballard P C Granberg P & Ballard R A Glucocorticoid levels in maternal and cord serum after prenatal betamethasone therapy to prevent respiratory distress syndrome J Clin Invest *56* 1548 1975
3 Kauppila A Jouppila P Karvonen P Tuimala R & Ylikorkala O Effect of dexamethasone on blood levels of ACTH cortisol progesterone estradiol and estriol during late pregnancy Int J Gynaecol Obstet *14* 177 1976
4 Künzig H J & Geiger W Estrogens in biochemical methods for monitoring risk pregnancies Contr Gynec Obstet (Karger Basel) *2* 2 1976
5 Liggins G C & Howie R N A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants Pediatrics *50* 515 1972
6 Ohrlander S Gennser G M & Grennert L Impact of betamethasone load given to pregnant women on endocrine balance of fetoplacental unit Am J Obstet Gynecol *123* 228 1975

7 Simmer H S Frankland M & Greipel M On the regulation of fetal and maternal 16α hydroxydehydroepiandrosterone and its sulfate by cortisol and ACTH in human pregnancy at term Am J Obstet Gynecol *121* 646 1974
8 Ylikorkala O Kauppila A & Tuimala R Effect of dexamethasone on serum levels of human placental lactogen during the last trimester of pregnancy J Obstet Gynaecol Br Commonw *81* 368 1974

Submitted for publication October 19 1977

Jan Martin Maltau
Department of Obstetrics and Gynecology
Rikshospitalet
Oslo
Norway

Acta Obstet Gynecol Scand 58:239–244 1979

SERUM AND AMNIOTIC FLUID HEAT LABILE ALKALINE PHOSPHATASE AND AMINOTRANSFERASES IN ASSOCIATION WITH MECONIUM STAINED LIQUOR

On their origin distribution and clinical use

I Thaler O Zinder H Abramovici and J M Brandes

From the Departments of Obstetrics and Gynecology and Clinical Biochemistry Rambam Medical Center Faculty of Medicine Technion Institute of Technology Haifa Israel

Abstract A method for detecting meconium in the amniotic fluid is described Samples of maternal serum cord serum and amniotic fluid were tested for alkaline phosphatase and transaminases activity in 32 healthy term gravidas during labor in whom meconium stained amniotic fluid was found The values obtained were compared to those of a control group consisting of 32 normal term pregnancies in whom the amniotic fluid was clear

Mean alkaline phosphatase activity was significantly higher in the study group in all three compartments maternal fetal and amniotic fluid

A significant and positive correlation between levels of alkaline phosphatase in the amniotic fluid and in maternal serum was found in the study group Alkaline phosphatase value of 550 IU/L or more in maternal serum was diagnostic and levels between 350–500 IU/L were highly suggestive for the presence of menconium in the amniotic fluid

Mean levels of transaminases (SGOT and SGPT) were similar in the two groups and all were within normal range The origin of alkaline phosphatase and the mode of transfer of the three enzymes are also discussed

It is suggested that this method can also be used during the third trimester of pregnancy

The significance of the passage of meconium during labor has always been contentious (1 4 10) It is agreed that in many cases it may reflect a state of fetal anoxia and early recognition is important for fetal welfare (16 21)

Brandes *et al* (7) described a non invasive technique for detecting meconium staining of amniotic fluid during labor by measuring levels of alkaline phosphatase in maternal serum using the Bessey Lowry method We have attempted in this study to test the results using a different method (centrifugal fast analysis) and at the same time to correlate the levels of alkaline phosphatase in the maternal and fetal serum and in the amniotic fluid We have also measured simultanously liver transaminases (SGOT and SGPT) in the three compartments First to compare their pattern of distribution with those of alkaline phosphatase in order to learn about the mode of transfer if any of the latter from one compartment to another and second to rule out liver disease or damage as the cause of alkaline phosphatase elevation

MATERIAL AND METHODS

The study group consisted of 32 healthy term gravidas who had uncomplicated pregnancies and in whom meconium stained liquor was found upon rupture of the amniotic sac during labor The control group matched for parity and age consisted of 32 healthy term gravidas who also had uncomplicated pregnancies and in whom the amniotic fluid was clear during labor

Amniotic fluid samples were collected through an amnioscope during artificial rupture of the membranes or through an intra amniotic polyethylene catheter if the membranes ruptured spontaneously All samples were collected during the first stage of labor and according to Sutcliffe (19) are assumed to be typical of the rest of the amniotic fluid Maternal venous blood was collected simultaneously and fetal cord blood was collected just after delivery

All sera were separated and immediately refrigerated as were the amniotic fluid supernatants Enzymatic determinations were carried out within 48 hours using Bergmeyer s method (6) for SGOT (aspartate aminotransferase) and SGPT (alanine aminotransferase) and p-nitrophenyl phosphate as the substrate for determining alkaline phosphatase activity (9) All assays were carried out by an automated analysis (Gemsaec Centrifugal Fast Analyzer Electro-Nucleonics U S A) Normal ranges of adult females and of newborn for those enzymes are presented in Table I

Table I *Normal range of transaminases and alkaline phosphatase in newborns and adult females (expressed in international units per liter)*

	Newborn	Adult Female
SGOT	5–120	5– 18
SGPT	5–120	5– 21
Alkaline Phosphatase	170–450	60– 40

Table II *SGOT levels (international units per liter) in maternal and fetal sera and in amniotic fluid*

	Mother	Fetus	Amniotic fluid	Mother	Fetus	Amniotic fluid
Subjects	31	29	27	32	28	28
Total range	6–39	7–53	6–36	6–42	5–75	5–32
Mean	15 6	28 2	14 7	15 5	28 8	14 5
S E	2 8	5 2	2 8	2 7	5 4	2 7

S E = Standard error of the mean

RESULTS

The mean levels and the standard error of the mean of transaminases (SGOT and SGPT) in amniotic fluid fetal and maternal sera from the two groups (the group of meconium stained liquor and the control group of clear amniotic fluid) are presented in Tables II and III

Table IV represents the values obtained for alkaline phosphatase The mean levels of the transaminases (SGOT and SGPT) were similar in the two groups in maternal serum fetal serum and amniotic fluid respectively and all were within normal range Fig 1 Mean alkaline phosphatase levels were significantly higher in the maternal and fetal sera of the study group as compared to those of the control group ($p<0$ 05) Mean alkaline phosphatase levels in the meconium stained liquor were 13 fold greater than n the clear amniotic fluid this being a highly ificant difference Fig 2

significant positive correlation (r=0 64 0 0005) was found in the study group between levels of alkaline phosphatase in the amniotic fluid and the maternal serum We did not find such a correlation in the control group Fig 3 We have also found a positive and significant correlation (r=0 54 p=0 007) between alakaline phosphatase levels in the fetal serum and the amniotic fluid of the study group but none in the control group Fig 4 When we compared levels of alkaline phosphatase in maternal sera to those of fetal sera in the study group a highly significant correlation was found (r=0 7 p= 0 0003) A positive and significant correlation was also demonstrated in the control group (r=0 48 p=0 004) Fig 5

We have also compared levels of transaminases (SGOT and SGPT) in the amniotic fluid to those in maternal and fetal sera and transaminase levels in fetal sera to those of maternal sera in each of the two groups (study and control) A significant and positive correlation existed between fetal and maternal serum in the group of meconium stained liquor (r=0 48 p=0 005 for SGOT and r=0 49 p=0 005 for SGPT) No correlation was found between maternal and fetal sera regarding SGOT levels in the study group and small correlation regarding levels of SGPT (r=0 43 p=0 01)

DISCUSSION

Though meconium excretion is sometimes observed under conditions of temporarily increased vagal tone (e g pressure on the fetal head umbilical cord compression) (10) its passage into the amniotic sac is still considered an indication of possible fetal jeopardy

Vorherr (20) in a prospective study on 1 000 gravidas noted a 19 fold increase in perinatal mortality and 4 4 fold increase in low Apgar score in cases where meconium was detected before labor Doring (8) found the incidence and degree of acidosis measured in cord blood of newborn infants to be increased after meconium release prior to delivery The early detection of meconium stained liquor has proved a valuable adjunct to the prompt recognition of an

Table III *SGPT levels (international units per liter) in maternal and fetal sera and in amniotic fluid*

	Group with clear amniotic fluid			Group with meconial amniotic fluid		
	Mother	Fetus	Amniotic fluid	Mother	Fetus	Amniotic fluid
Subjects	31	29	27	31	26	27
Total range	5–22	5–37	2–43	4–21	4–68	3–40
Mean	9 96	11 7	9 11	10	12 88	9 88
S E	1 8	2 2	1 8	1 8	2 5	1 9

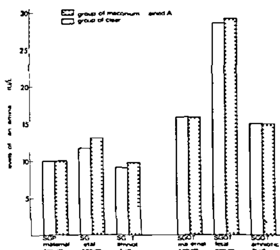


Fig 1 Mean levels of transaminases (SGOT and SGPT) in maternal and fetal serum and in amniotic fluid of the two groups

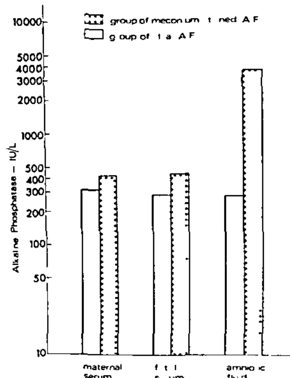


Fig 2 Mean alkaline phosphatase levels in maternal and fetal serum and in amniotic fluid of the two groups Drawn on a semilogarithmic scale

acidotic fetus the selection of cases for intensive fetal monitoring and the reduction of intra partum asphyxial damage (16) This may also avoid fetal death (15) and warn the physician of the danger of meconium aspiration The commonly employed methods for detecting meconium in the amniotic sac namely amnioscopy amniocentesis and amniotomy are all invasive not always informative and cannot be applied in all situations

Jonassen (11) noted that in normal pregnancies where meconium stained liquor was found a probably significant correlation existed between the alkaline phosphatase activities in amniotic fluid and maternal serum ($r = 0.37$ $p < 0.05$) but he postulated this enzyme to be of placental origin Brandes (7) was the first to put into clinical use Jonassen s observation that meconium stained liquor contains markedly elevated alkaline phosphatase activity exceeding normal levels 20–400 times He found most of this enzyme to be in heat labile form and that the rise in its activity in maternal and fetal blood seen in conjunction with meconium stained liquor is mainly due to this heat labile fraction which is derived from the meconium itself Heat stable alkaline phosphatase which is of placental origin is found only in small amounts in the amniotic fluid (7) but more so in fetal blood less than 10 per cent of the total (17) Brandes (7) found a highly significant correlation between levels of heat labile alkaline phosphatase in amniotic fluid and maternal serum ($r = 0.56$ $p = 0.001$) in cases where meconium stained liquor was found He found no correlation between heat stable alkaline phosphatase levels in maternal serum and total alkaline

Table IV *Alkaline phosphatase (international units per liter) in maternal and fetal sera and in amniotic fluid*

	Group with clear amniotic fluid			Group with meconial amniotic fluid		
	Mother	Fetus	Amniotic fluid	Mother	Fetus	Amniotic fluid
Subjects	32	30	27	28	26	23
Total range	97–519	147–396	46–570	127–1 545	87–1 767	494–14 980
Mean	310	276	272	415	435	4 635
S E	54 8	50 4	52 3	75 8	85 3	966

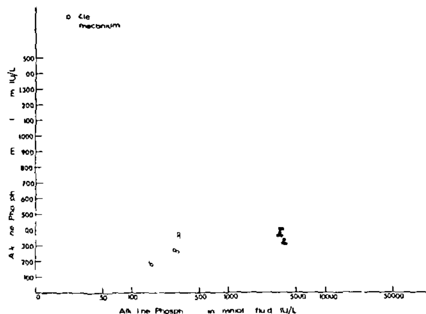


Fig 3 The relation between levels of alkaline phosphatase in maternal sera and in amniotic fluid of the two groups Drawn on a semilogarithmic scale

phosphatase levels in the amniotic fluid We found in this study a highly significant correlation between the alkaline phosphatase activities in the amniotic fluid and in the maternal serum in cases of meconium stained liquor ($r=0.64$ $p=0.0005$) (fig 3) while no correlation was found in the control group Mean maternal alkaline phosphatase levels differed gnificantly ($p<0.05$) between the two groups

Both studies using different methods of enzymatic ssays show a significant correlation between maternal serum and amniotic fluid alkaline phosphatase in cases of meconium stained liquor Total alkaline phosphatase activity in maternal serum can be used therefore as a predicitve index for meconium stained liquor From fig 3 it can be seen that maternal alkaline phosphatase levels exceeding 550 IU (in absence of toxemia liver disease or bone disease) is diagnostic for meconium stained liquor and levels between 350–550 IU are highly suggestive for its presence in the amniotic sac (the probability for clear amniotic fluid in those cases being less than 0.05)

This method for detecting meconium in the am

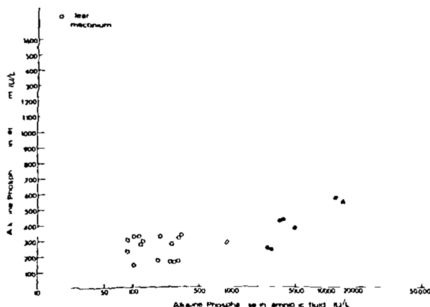


Fig 4 The relation between levels of alkaline phosphatase in amniotic fluid and in fetal serum of the two groups Drawn on a semilogarithmic scale

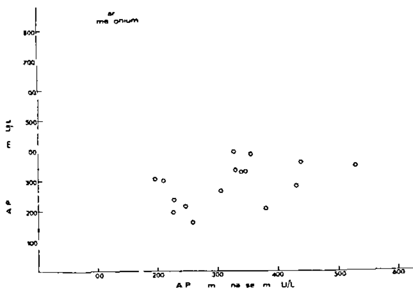


Fig 5 The relation between levels of alkaline phosphatase in maternal and fetal seram of the two groups

niotic fluid can be extended to abnormal pregnancies as well since no difference was found between values of heat stabile alkaline phosphatase in normal and abnormal pregnancies (2 14) excluding toxemia where the heat stable enzyme is sometimes markedly elevated (18) Here one needs to measure the heat labile fraction in maternal serum in order to predict the presence of meconium

A significant correlation also existed between the alkaline phosphatase activities in amniotic fluid and fetal serum ($r=0\ 54$ $p=0\ 007$) in the study group but not in the control group Fig 4 These facts suggest that after meconium excretion the alkaline phosphatase is dissolved in the amniotic fluid and part of it s transferred to maternal and fetal serum

A highly significant correlation existed between levels of alkaline phosphatase in maternal and fetal sera ($r=0\ 7$ $p=0\ 00003$) in the study group and a significant correlation in the control group ($r=0\ 48$ $p=0\ 004$) Fig 5 This suggests a common route of alkaline phosphatase transfer from the amniotic fluid to both maternal and fetal serum and is in contrast to the findings of Beck (3) and Kitchener (12) who found no such correlation

Although the elevation of alkaline phosphatase in the serum is probably not due to simple leakage of the enzyme from damaged cells (13) this is the rule for glutamic oxaloacetic and glutamic pyruvic transaminases (SGOT and SGPT respectively) We measured these enzymes in the three compartments in order to compare their pattern of distribution with those of alkaline phosphatase as all are proteins of high molecular weight In addition the question arose whether in cases of meconium excretion the elevation of alkaline phosphatase might be due to liver damage (e g hypoxia congestion) Transaminases are sensitive indicators of liver damage and were used here in this respect as well

Mean fetal and maternal levels of both SGOT and SGPT were found to be within normal range and of similar levels in both groups (study and controls) Tables II and III The results resemble those of previous studies (5 13) all excluding liver dysfunction during normal pregnancy

Mean SGOT levels in cord blood were nearly twice those in maternal serum and in amniotic fluid (as has also been shown by Lapan and Friedman) (13) while cord blood levels of SGPT were only slightly elevated above the other compartments

We found in the group with meconium stained liquor a positive correlation between transaminase levels in maternal and fetal compartment while no such correlation was found for SGOT and a much lesser one for SGPT in the control group with clear amniotic fluid

The results obtained for the transaminases and especially those obtained for alkaline phosphatase strongly point towards the possibility of altered permeability for these large molecules after meconium excretion The placenta and fetal membranes are a barrier that may be damaged or altered by the circumstances that also bring about meconium release

by the fetus (e g hypoxia) thus enabling the passage of larger molecules in much the same way as the glomerulus of the damaged kidney allows the passage of large proteins

This paper describes a new method for the early detection of meconium in the amniotic sac We have extended this method to pregnant women in labor in cases where the membranes were still intact as well as to pregnant women who were not in labor through the third trimester of pregnancy and have found that the correlation between high maternal alkaline phosphatase and meconium stained liquor (found by amniocentesis) persists (unpublished data)

We feel that this method serve as a screening procedure for high risk pregnancies for locating those cases where the fetus might already be jeopardized (as expressed by meconium in the liquor) This might be expected to improve perinatal outcome

REFERENCES

1 Abramovici H Brandes J M Fuchs K & Timor Tritsch I Meconium during delivery a sign of compensated fetal distress Am J Obstet Gynecol *118* 251 1974
2 Aoba H Yukichi H & Ryuji Y Serum heat stabile alkaline phosphatase in normal and abnormal pregnancy *Tohoku J Exp Med 91* 201 1967
3 Beck F I & Clarck L C Plasma alkaline phosphatase II normative data for pregnancy Am J Obstet Gynecol *60* 731 1950
4 Benirschke K Diseases of the placenta *In* Modern *Perinatal medicine (ed L Gluck)* p 102 Year Book Medical Publishers Inc 1974
5 Borglin W E Serum transaminase activity in uncomplicated and complicated pregnancy and in newborns J Clin Endocrinol Metab *18* 872 1958
6 Bergmeyer H U & Bernt E Method of enzymatic analysis (ed H U Bergmeyer) pp 769 864 Verlag Chemie Weinheim and Academic Press Inc New York and London 1974
7 Brandes J M Atad J & Zuckerman H High maternal serum alkaline phosphatase as an index of meconial amniotic fluid Biol Neonate *31* 283 1977
8 Doring G K Gynäkologie und Geburtshilfe (eds D Käser *et al*) p 534 Vol 2 Georg Thieme Verlag Stuttgart 1967
9 Hausamen T U Helger R Rick W & Gross W Optimal Conditions for the determination of serum alkaline phosphatase by a new kinetic method Clin Chim Acta *15* 241 1967
10 Hon E H Observations on pathologic fetal bradycardia Am J Obstet Gynecol *77* 1084 1959
11 Jonassen L E The clinical value of amniotic fluid analysis in pregnancies complicated by Rh immunization or hepatosis Acta *Obstet Gynecol* Scand *52* 113 1973
12 Kitchener P N Francis C N & Posen S Alkaline phosphatase in maternal and fetal sera at term and during the puerperium Am J Clin Pathol *44* 654 1965
13 Lapan B & Friedman M M A comparative study of fetal and maternal serum enzyme levels J Lab Clin Med *54* 417 1959
14 Leroux M & Perry W F Serum heat stabile alkaline phosphatase in pregnancy Am J Obstet Gynecol *108 235 1970*
15 Mandelbaum B Gestational meconium in the high risk pregnancy Obstet Gynecol *42* 87 1973
16 Matthews C D & Martin M R Early detection of meconium stained liquor during labour a contribution to fetal care Am J Obstet Gynecol *120* 808 1974
17 Quigley G J Richard S R T & Shier K J Heat stabile alkaline phosphatase Am J Obstet Gynecol *106* 340 1970
18 Sammour M B Ramadan M A & Khalil F K Serum and placental lactic dehydrogenase and alkaline phosphatase isoenzymes in normal pregnancy and in pre eclampsia Acta Obstet Gynecol Scand *54* 393 1975
19 Sutcliffe R G Brock D J H & Robertson J G Enzymes in amniotic fluid a study of specific activity patterns during pregnancy J Obstet Gynecol Br Commonw *79* 895 1972
20 Vorherr H Placental insufficiency in relation to post term pregnancy and fetal post maturity Am J Obstet Gynecol *123* 67 1975

Submitted for publication September 29 1977

I Thaler M D
Department of Obstetrics and Gynecology
Rambam Medical Center Faculty of Medicine
Technion Institute of Technology
Haifa
Israel

Acta Obstet Gynecol Scand 58 245–248 1979

SERUM PROLACTIN AND THYROID STIMULATING HORMONE LEVELS FOLLOWING THYREOTROPIN RELEASING HORMONE STIMULATION IN PREECLAMPTIC PATIENTS

S Kulseng Hanssen P A Torjesen K F Hanssen

From the Department of Obstetrics and Gynecology Hormone and Isotope Laboratory Medical Department B Aker Hospital Oslo 5 Norway

Abstract Serum prolactin and thyroid stimulating hormone (TSH) levels were measured following administration of thyreotropin releasing hormone (THR) in 17 preeclamptic patients and 18 normal pregnant controls

From the 31st to the 35th pregnancy week the preeclamptic patients showed increased basal serum prolactin and TSH levels compared to controls but later in pregnancy the differences disappeared Following TRH stimulation the serum prolactin and TSH responses were similar in women with and without preeclampsia A possible role of prolactin in the development of preeclampsia is discussed

Preeclampsia is characterized by elevated blood pressure sodium and water retention (4) and impaired renal function which is usually associated with proteinuria and elevated uric acid Excess circulating pressor or fluid retaining agents related to the renin angiotensin aldosterone system and desoxycorticosterone have not been identified in preeclampsia (16) As prolactin reveals sodium and water retaining abilities in lower vertebrates (6) it has been suggested to play a role in the development of preeclampsia in man (7 9) In keeping with this Redman *et al* (11) demonstrated significantly higher serum prolactin levels in pregnant women with elevated blood pressure proteinuria and/or edema However most of the patients had been treated with drugs that might influence the prolactin secretion

We have studied serum prolactin levels following thyreotropin releasing hormone (TRH) stimulation in patients with preeclampsia and in normal pregnant controls These patients did not receive drugs known to influence the prolactin secretion Furthermore we studied the serum thyroid stimulating hormone (TSH) response to TRH stimulation in the same patients as it has been suggested that TSH levels are elevated in preeclamptic patients (8)

PATIENTS AND METHODS

Seventeen patients with preeclampsia and 18 control patients with uncomplicated pregnancy were studied Preeclampsia was diagnosed in the presence of at least two of the following signs Blood pressure higher than 140/90 on two occasions measured at least 12 hours apart edema and proteinuria Edema was graded from 0 to 3 according to severity and recorded as the sum of the gradings in face fingers and ankles Apart from one of the control subjects who had used trichlormethiazide and 5 of the preeclamptic subjects who had used other diuretics (polythiazide hydrochlorothiazide or furosemide) none of the patients or the controls received drugs Furosemide probably does not influence prolacting secretion (2 3) No data about the effect of polythiazide hydrochlorothiazide and trichlormethiazide on serum prolactin levels have been published In order to study a possible effect of these thiazides on prolactin the serum prolactin levels following TRH stimulation were measured in normal nonpregnant female volunteers who had received the drugs for three days in doses used for preeclamptic treatment Each thiazide was given to three volunteers leading to basal and stimulated prolactin levels within the normal range

All the women with preeclampsia and the controls were laying in patients and gave their informed consent A teflon cannula was placed in a forearm vein on the evening before the test to avoid psychological stress The patients were kept in bed until completion of the test and they were allowed a minor fluid intake only The test was started between 6 30 and 8 00 a m and 500 μg TRH (Roche) was given rapidly intravenously at time zero Blood samples were taken for measurement of serum prolactin and TSH levels at 30 minutes before and zero 15 30 and 60 minutes after the TRH administration All the patients were clinically euthyroid Serum was removed from the clot as soon as possible and frozen at minus 20 C until analyzed The basal serum prolactin and TSH levels were the values obtained at zero minutes The response to the TRH stimulation (S) was calculated as Δ of the sum of the serum levels at 15 30 and 60 minutes after the TRH injection minus the basal level Because serum prolactin levels increase during pregnancy (15) the patients were divided into 3 groups 31 35 weeks 36-38 weeks and 39-41 weeks of pregnancy Serum uric acid was determined by a standard method Pro-

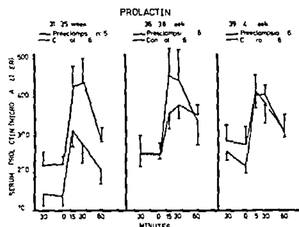


Fig 1 Serum prolactin levels following 500 µg TRH intravenously in preeclamptic patients and pregnant controls at 31 35 36-38 and 39-41 weeks of pregnancy (mean ±SEM)

teinuria was measured according to Esbach Serum TSH (14) and prolactin (12) levels were determined by radioimmunoassay

Statistical evaluation was performed using non parametric tests Wilcoxon rank sum test and Spearman correlation analysis (5 13) Clinical and chemical data about the patients are given in table I

RESULTS

serum prolactin levels are depicted in figures 1 d 2 The basal prolactin levels in the 31 35 week group were significantly higher (p<0 05) in preeclamptic patients 219±21 µg/l compared to control patients 140±26 µg/l (mean ±SEM) In the 36-38 and 39-41 week groups no differences were found The serum prolactin response 30 minutes following TRH stimulation in the 31 35 week group was significantly higher (p<0 025) in preeclamptic patients 439±63 µg/l compared to controls 270±43 µg/l But the serum prolactin response (S) following TRH stimulation was between 95 and 162 µg/l in the three groups and no significant difference was observed between preeclamptic patients and controls

No correlation was found between basal serum prolactin and diastolic blood pressure uric acid levels proteinuria and edema score (Spearman correlation analysis)

The serum TSH levels are depicted in figures 3 and 4 The preeclamptic patients in the 31 35 week group had a significantly higher (p<0 025) basal serum TSH level 2 6±0 1 µg/l compared to controls 2 0±0 2 µg/l In the 36-38 and 39 41 week groups no differences were observed The serum TSH response (S) following TRH stimulation did not differ significantly between preeclamptic patients and controls

The mean TSH response in the various groups was between 1 0 and 1 5 µg/l

DISCUSSION

Our findings in the 31 35 week group are in accordance with Redman *et al* (11) who demonstrated significantly higher serum prolactin levels in 32nd week hypertensive pregnant patients with either proteinuria or edema than in those without these features In

Table I *Clinical and chemical data on the patients studied*

Group	No	Age Years Mean	Duration pregnancy days Mean	Blood pressure mm Hg Mean	Proteinuria g/l Esbach Mean±SEM	Edema score Mean	Uric acid micro mol/l Mean±SEM
Preeclampsia 31−35 weeks	5	26 0	235	143/101	2 4 ± 1 3	1 6	446 ± 55
Normal pregnancy 31−35 weeks	6	28 5	232	113/73	0 1 ± 0 1	0	238 ± 18
Preeclampsia 36−38 weeks	6	26 8	261	1[illegible]0/108	0 8 ± 0 4	2	458 ± 36
Normal pregnancy 36−38 weeks	6	27 7	259	122/76	0	0 5	29[illegible] ± 18
Preeclampsia 39−41 weeks	6	23 5	275	151/107	0 3 ± 0 1	3 8	446 ± 18
Normal pregnancy 39−41 weeks	6	25 8	275	117/77	0 1 ± 0 1	0 2	315 ± 12

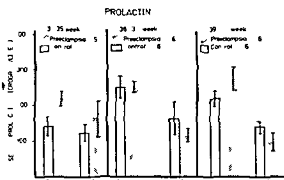


Fig 2 Basal serum prolactin levels and prolactin response S (calculated as ⅓ of the sum of the prolactin values at 15 30 and 60 minutes minus the basal value) following 500 µg TRH intravenously at time zero of the 31 35 36-38 and 39-41 week groups (mean ±SEM)

their study the highest level for serum prolactin was demonstrated in patients with a rising serum urate level However most of their patients were treated with drugs that might influence serum prolactin levels (α methyldopa barbiturates and benzodiazepines) Biswas and Rodeck (1) did not find any difference in fasting basal serum prolactin levels between preeclamptic and normal pregnant patients but they did not state when in pregnancy the samples were taken

In our study the serum prolactin levels in preeclampsia were only significantly higher compared to controls early in the third trimester of pregnancy The reason for this might be that preeclampsia which starts early in pregnancy is usually more severe than preeclampsia at the end of pregnancy Three of our five patients in the 31 35 week group had to be delivered by cesarean section before term because of serious preeclampsia compared to only one of 12 patients in the 36-41 week groups Prolactin might possibly play a role in the development of preeclampsia but the increased serum prolactin levels of the preeclamptic patients in the 31 35 week group could also be due to stress (10)

Genazzani *et al* (8) reported increased TSH plasma levels in preeclampsia compared to normal pregnancy from the 21st to the 41st week of pregnancy Our preeclamptic patients had higher basal serum TSH levels compared to controls only in the 31 35 week group not later in pregnancy

It is interesting that both basal prolactin and TSH levels were significantly higher in 31 35 week preeclamptic patients compared to controls This might suggest that the reason is other than stress

Following TRH stimulation the serum prolactin and TSH responses were not statistically different in preeclamptic patients and controls This suggests that the ability of the pituitary to secrete prolactin and TSH in response to TRH administration is unaffected in preeclampsia

REFERENCES

1 Biswas S & Rodeck C H Plasma prolactin levels during pregnancy Br J Obstet Gynecol *83* 683 1976
2 Branch R A Cole E N Aviy R Levine D & Ramsay L Prolactin frusemide and renal function in normal man J Endocrinol *67* 59 1975
3 Buckman M T & Peake G T Osmolar control of prolactin secretion in man Science *181* 755 1973
4 Chesley L C Sodium retention and preeclampsia. Am J Obstet Gynecol 95 127 1966
5 Documenta Geigy Scientific Tables (ed K Diem & C Lentner) p 192 Ciba Geigy Ltd Basel 1975
6 Endsor D M & Ball I N Prolactin and osmoregulation in fishes Fed Proc *31* 1615 1972
7 Friesen H G Fournier P & Desjardins P Pituitary prolactin in pregnancy and normal and abnormal lactation Clin Obstet Gynecol 16 no 3 25 1973
8 Genazzani A R Fioretti P & Lemarchand Beraud Th Plasma thyreotropin levels during pregnancy J Obstet Gynecol Br Comm *78* 117 1971
9 Horrobin D F The possible role of prolactin in preeclampsia Med Hypothesis *1* 159 1975
10 Noel G L Suh H K Stone J G & Frantz A G Human prolactin and growth hormone release during surgery and other conditions of stress J Clin Endocrinol Metab *35* 840 1972

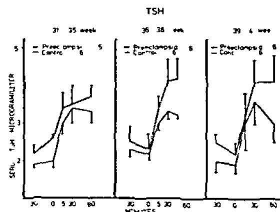


Fig 3 Serum TSH levels following 500 µg TRH intravenously in preeclamptic patients and pregnant controls at 31 35 36-38 and 39-41 weeks of pregnancy (mean ±SEM)

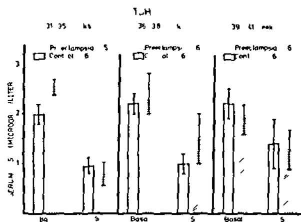


Fig 4 Basal serum TSH levels and prolactin response S (calculated as ⅓ of the sum of the prolactin values at 15 30 and 60 minutes minus the basal value) following 500 µg TRH intravenously at time zero of the 31 35 36-38 and 39 41 week groups (mean ±SEM)

11 Redman C W G Bonnar J Beilin L J & McNeilly A S Prolactin in hypertensive pregnancy Br Med J *1* 304 1975

12 Rutlin E Haug E & Torjesen P A Serum thyreotropin prolactin and growth hormone response to TRH during oestrogen treatment Acta Endocrinol 84 23 1977

13 Siegel S Nonparametric statistics for the behavioral sciences International student edition McGraw Hill Kogakusha New York Tokyo

14 Torjesen P A Haug E & Sand T Effect of thyreotropin releasing hormone on serum levels of pituitary hormons in man and women Acta Endocrinol 73 455 1973

15 Tyson J E Hwang P Guyda H & Friesen H G Studies of prolactin secretion in human pregnancy Am J Obstet Gynecol *113* 14 1972

16 Weir R J Doig A Fraser R Morton J J Parboosingh J Robertson J I S & Wilson A *In* Hypertension in pregnancy p 251 John Wiley & Sons New York 1976

Submitted for publication November 14 1977

S Kulseng Hanssen M D
Department of Obstetrics and Gynecology
Ullevål Hospital
Oslo
Norway

Acta Obstet Gynecol Scand 58 249–253 1979

EFFECT OF INDUCTION OF GENFRAL ANESTHESIA FOR CESAREAN SECTION ON INTERVILLOUS BLOOD FLOW

Pentti Jouppila Jyrki Kuikka Riitta Jouppila and Arno Hollmen

From the Departments of Obstetrics and Gynecology Anesthesiology and Clinical Chemistry University of Oulu Oulu Finland

Abstract Intervillous blood flow was measured by a new intravenous ^{133}Xe method before and during induction of general anesthesia for cesarean section in 10 healthy mothers The flow values showed a highly significant decrease ($p<0\ 001$) (35 per cent on an average) at the time of anesthesia compared with the control values The impairment was observed in all the cases The role of the maternal changes in hemodynamic parameters and acid base balance as a background of this decrease is discussed

General anesthesia has maintained its position as the most widely used anesthetic for cesarean sections Provided that placental function is satisfactory and small doses of anesthetic agents are used anesthesia does not seem to modify the condition of the infants (5 14) although they can be affected in proportion to the depth and probably also the duration of anesthesia (8 15) Thiopentone the most widely used agent for intravenous induction of anesthesia for cesarean sections has several maternal cardiovascular effects It causes a decrease in cardiac output and stroke volume and an increase in heart rate (6 7) The effect on mean arterial blood pressure is minimal The circulatory changes are considered to be due to a combination of factors including peripheral vasodilatation myocardial depression and depression of the vasomotor center

A single injection of thiopentone has been shown to reduce uterine blood flow by 15 per cent in pregnant ewes (22) The measurement of human placental blood flow has been a difficult problem in obstetrical practise The methods developed on the basis of temperature variations in cervical tissues (2) have been shown to be inaccurate (18) Different radionuclide methods using intravenously injected non diffusible tracers represent the placental blood flow only qualitatively Until now the use of diffusible tracers has only been possible by direct injection into the intervillous space (3 4) Recently Rekonen *et al* (17) developed a new method for quantitative measurement of human intervillous and myometrial blood flow The method is based on the use of intravenously injected ^{133}Xe

The aim of this study was to examine the effect of the method used routinely in the induction of general anesthesia for cesarean section on intervillous blood flow

MATERIAL AND METHODS

Patients The series collected during the six months period from December 1976 to May 1977 consisted of 10 healthy mothers between the 37th–41st week of pregnancy with no signs of disturbance of the fetoplacental unit The indication for cesarean section was a narrow pelvis in seven cases and a previous cesarean section in three cases The mothers were not experiencing spontaneous uterine contractions at the time of operation

Before induction of anesthesia the mothers were lying on the operating table for about 30 min in at least a 15 C left lateral tilted position which was maintained during the operation During this time period the control measurement of placental blood flow was performed The placenta was localized in advance using an ultrasonic B-scan Only patients with the placenta on the anterior uterine wall were accepted and the placental area was marked on the abdominal skin The study and its purpose were explained to the mothers and their consent was obtained

Anesthetic method The patients were unpremedicated 0 5 mg atropine i v was given before induction of anesthesia with thiopentone (4 mg/kg) i v After disappearance of corneal reflexes 1 mg/kg of succinylcholine i v was given for intubation When the patient was relaxed she was ventilated with pure oxygen 2 ml of ^{133}Xe (see below) was rapidly injected into the antecubital vein during which time and for 15 sec afterwards the patient was not ventilated Thereafter the mother was intubated and anesthesia was maintained with 50 per cent N O in O and 0 2 per cent succinylcholine infusion was started

^{133}Xe Methods The method used here has been discussed in detail by Rekonen *et al* (17) About 2 mCi of ^{133}Xe in saline was rapidly injected through a two-way cannula and flushed immediately with 10 ml of saline The subject held her breath during the first measurement for about 15 s in order to ensure that part of the tracer bolus bypassed the lungs During the second measurement this co-operative procedure was replaced by the non ventilating period of

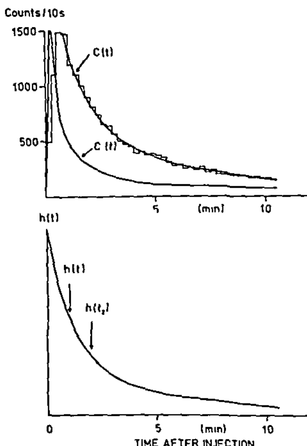


Fig 1 a The step curve represents the measured placental rve and the solid line indicated the fitted curve (C(t)) (t) is the measured arterial input curve (left ventricle) *I B* The corresponding recirculation corrected curve 1) The 1 2 minute interval of this curve is for calcula n of the initial slope index – 100 × ln(h(t)) ln(h(t₁))]

about 15 s The progress of the tracer over the placental site which had previously been localized by a B scan was measured with a scintillation detector The diameter of the measuring area at the depth of the placenta was about 10 cm and the crystal to-skin distance was about 20 cm The channel width used was 10 s and the measuring time 10 min before the anesthesisa and 3 min during the induction of anesthesia

Calculations *A two compartmental analysis* was carried out using the following equation

$$C(t) = \sum_{i=1}^{2} A_i k_i e^{-k_i t} \int_0^t C_A(u) e^{k_i u} du \qquad 0 < t \leq 10 \text{ min} \quad (1)$$

(Fig 1 A and B)

where $C(t)$ = count rate obtained over the placenta at time t
t = time after the injection of the tracer
A_i = scale factor
k_i = transfer rate constant of the i th component
$C_A(t)$ = concentration of ^{133}Xe in expired air at time t

Index 1 refers to the blood flow of the intervillous space and index 2 to the blood flow of the myometrium

Intervillous blood flow was calculated according to the equation $F_1 = 100 \times k_1$ (ml/min/100 ml) ( )
and myometrial blood flow as follows

$$F = 70 \times k_2 \text{ (ml/min/100 g)} \quad (3)$$

where 70 ml/100 g = partition coefficient between the blood and the myometrium

As only the first three minutes during anesthesia (II) were recorded the comparison between the flow values before (I) and during (II) anesthesia was made using the initial slope method (ISI) as follows

$$F_{1II} = \frac{ISI_{II}}{ISI_I} F_{1I} \quad (4)$$

where the initial slope index was determined from equation (1) at a time interval of 1 0 – 2 0 min after injection of the tracer

It was obviously impossible to obtain the myometrial blood flow value during anesthesia owing to the relative short measuring period (3 min)

Maternal arterial acid base balance was determined during the two placental blood flow measurements as was maternal pulse rate and arterial blood pressure Acid base balance values were also determined from the umbilical vein blood obtained before clamping the cord The induction delivery intervals and the Apgar scores of the newborn infants at 1 and 15 min were recorded

The statistical analysis were performed using Student s t test

RESULTS

The individual values of intervillous blood flow before and during induction of anesthesisa are presented in Fig 2 The values recorded at the time of induction ranged between 22 50 per cent of the values obtained before anesthesia The mean intervillous blood flow before induction was 131±57 ml/min/100 ml and that during induction 84±37 ml/min/100 ml

Table I *Individual values of maternal heart ra e and arterial blood pressure before and during induction of anaesthesia*

Patient	Pulse rate		Arterial blood pressure	
No	Before	During	Before	During
1	107	100	130/70	150 95
2	100	150	170/80	170/90
3	119	160	140/90	130/90
4	60	145	110/70	110/80
5	75	100	130/90	150/100
6	85	110	130/90	150/100
7	110	110	170/90	[illegible]10/100
8	80	115	120/80	140/100
9	124	100	150/100	165/130
10	114	110	160/100	180/1 0
Mean	97	120	135/85	150/100
SD	±20	±2[illegible]	±20/10	±30/15

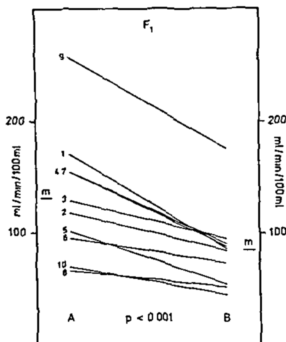


Fig 2 The individual intervillous flow changes A = before anaesthesia B = during induction of anaesthesia m = mean value

The difference between these means was highly significant ($p<0\ 001$) The myometrial blood flow before induction was 9±2 ml/min/100 g

The individual maternal heart rates and arterial blood pressure values can be seen in Table I The pulse rates showed a tendency to increase (mean rise 24 per cent) The mean blood pressure increased slightly but insignificantly from the control values

The acid base balance of the mothers before being anesthetised was normal The mean arterial pCO_2 value was 26 3 mmHg before induction and 31 9 mmHg during induction The pH values of the mothers during induction were above 7 30 except in case No 3 (pH 7 28)

The induction delivery intervals varied between 5 20 and 14 30 min (mean 9 50) The acid base balance values of the umbilical vein blood 1 min after delivery and the Apgar scores in individual cases can be seen in Table II The acid base balance can be regarded as normal in all the newborns except in case No 3 where the baby showed signs of respiratory and metabolic acidosis The Apgar scores were seven or more for all the neonates

DISCUSSION

Placental blood flow in this study was measured using a new intravenous ^{133}Xe method This method can be regarded as highly suitable to clinical obstetrical practice and the reproducibility of the results in consecutive measurements is satisfactory (17) The radiation dose to the fetus is negligible (less than 1 mrad per examination) The values of intervillous blood flow obtained before the induction of anesthesia approximated to the results of Rekonen *et al* (17) (131∓56 and 135∓49 ml/min/100 ml respectively) *The initial slope method used here (Fig 2) is generally* accepted for the calculation of flow variations in different organs and thus it can be applied to the determination of possible changes in intervillous blood flow

Breath holding is a very important detail in the measurement of placental blood flow by this diffusible tracer During the induction of general anesthesia the patients were ventilated after muscle relaxation but the ventilation was discontinued for about 15 sec immediately after the second injection of ^{133}Xe Intubation took place therefore after 15 seconds apnea Thus the stopping of ventilation corresponds well to physiological breath holding at the first measurement The maternal arterial pCO_2 values during the second measurement also showed an increase indicative of slight hypoventilation

Our results showed that intervillous blood flow diminished highly significantly ($p<0\ 001$) during the induction of general anesthesia the decrease varying within 22 50 per cent The technique of induction of anesthesia used in this study is commonly accepted in connection with cesarean sections The second

Table II *The acid base balance (umbilical vein blood) and Apgar scores of newborn infants after cesarean section*

Newborn	Acid base balance				Apgar scores	
infant No	pH	pCO_2	BE	pO_2	1 min	15 min
1	7 29	45 8	− 5 0	29 3	9	9
2	7 35	44 3	− 5 7	34 5	9	9
3	7 13	54 8	−12 0	27 0	8	8
4	7 29	45 0	− 4 8	41 3	7	9
5	7 27	45 0	− 6 6	37 5	9	9
6	7 29	41 3	− 6 9	40 0	9	9
7	7 26	43 0	− 6 4	35 5	8	10
8	7 3	40 0	− 5 1	54 0	8	9
9	7 28	43 5	− 6 5	34 5	9	10
10	7.29	47 0	− 6 8	39 5	9	9
Mean	7 27	45 0	− 6 6	37 5		
SD	±0 06	±4 5	± 2 3	±8 3		

measurement of the intervillous blood flow was performed after the patient had received the sleeping dose of thiopentone and succinylcholine Intubation took place at the final stage of the second measurement In this situation after a small dose of thiopentone and only 50 per cent N_2O the subjects would have had a level of awareness which it could be suggested may have caused apprehension and a surge of catecholamines Catecholamines have been shown in high doses to cause vasoconstriction of the uterine arteries (1 19) and therefore diminish intervillous blood flow The role of endogenous catecholamines in this respect remains to be solved It seems unlikely that the blood levels of catecholamines were the cause of the present changes It has previously been shown that after thiopentone induction of anesthesia and after intubation the level of plasma cathecholamines does not change significantly (12 21)

Thiopentone and other barbiturate anesthetics have been shown to decrease cardiac output by 25 per cent due to peripheral vasodilatation causing pooling of blood in the extremities and a reduction of venous return to the heart (6) In an anesthetic dose thiopentone also causes a mild myocardial depression (16) Our own examinations using ^{133}Xe have shown that the mean pulmonary perfusion decreases during induction of anesthesia by 40 per cent According to our observation the decrease in cardiac output is not f the same magnitude (only ≤ 15 per cent) as that of rvillous blood flow It is possible that compen ry vasoconstriction of the splanchnic renal and ssibly also uterine arteries can account for the maintenance of normal or increasing blood pressure in our patients combined with a definite increase in the maternal pulse rate It is possible that uterine circulation participates in the female safety mechanisms via vasoconstriction This has also been observed in hemorrhage during pregnancy (10) Another explanation could be the rising maternal pCO_2 values during induction of anesthesia Blood flow in the brain has been observed to improve by 4 per cent in relation to an increase of 1 mmHg in arterial pCO_2 (13) The mean rise of pCO_2 in our patients was approximately 5 mmHg when the acid base values during the second ^{133}Xe measurement were compared with the control values Such short term hypercapnia can improve transiently cerebral blood flow during the induction of anesthesia and this could lead to a compensatory impairment of blood flow in some other organ e g the placenta

The usual reason for diminution of cardiac output and uterine circulation during late pregnancy is the maternal supine position Impairment of cardiac output in this position has been observed in as many as 50 per cent (20) of women This effect was carefully avoided in our measurements by using at least a 15 left lateral tilted position Thus the decrease in intervillous blood flow cannot be attributed to maternal position

Methodological reasons restricted the measurements of placental blood flow to the induction phase of anesthesia The possible roles of the inhalation agents (N_2O) and the time factor after commencement of anesthesia on blood flow cannot therefore be evaluated Muscle relaxants however do not seem to have any direct effect on the myocardium nor the blood vessels nor the the vasomotor center (9)

The highly significant decrease in placental blood flow observed in this study was not followed by delivery of depressed infants Only one pH value of umbilical vein blood at the time of cord clamping was at an acidotic level (7 13) with a low paO_2 and high pCO_2 values The decrease of intervillous blood flow (42 per cent) in this patient was slightly above the mean decrease in the whole series The Apgar scores were 8 at 1 min and 8 at 15 mins however All the other acid base balance values of umbilical vein blood were within the normal nonacidotic level Hence a healthy fetus seems to tolerate well a 22 50 per cent reduction of short duration in placental blood flow a finding which agrees with some earlier reports (11)

Our present findings justify the extension of such studies into the effects of different analgesic and anesthetic procedures on placental blood flow

REFERENCES

1 Barton M D Killam A P & Meschia G Response of ovine uterine blood flow to epinephrine and norepinephrine Proc Soc Exp Biol Med *145* 996 1974
2 Brotanek V Kazda S & Roth L A method for measurement of uterine blood flow in pregnant women Physiol Bohemoslov *11* 358 1962
3 Browne J C M & Veall N Maternal placental blood flow in normotensive and hypertensive women J Obstet Gynaec Brit Emp *60* 141 1953
4 Clavero J A Negueruela J Ortiz L do los Heros J A & Medgero S P Blood flow in the intervillous space and fetal blood flow Am J Obstet Gynecol *116* 340 1973
5 Crawford J S Anaesthesia for caesarean section proposal for evaluation with analysis of method Br J Anaesth *34* 179 1962

6 Etsen B & Li T H Haemodynamic changes during thiopental anesthesia in humans J Clin Invest *34* 500 1955

7 Fieldman E J Ridley R W & Wood E H Hemodynamic studies during thiopental sodium and nitrous oxide anesthesia in humans Anesthesiology *16* 473 1955

8 Finster M & Poppers P J Safety of thiopental used for induction of general anesthesia in elective cesarean section Anesthesiology *29* 120 1968

9 Foldes F F *In* Muscle relaxants in anesthesiology Springfield Ill Charles C Thomas 1957

10 Greiss F C Jr Uterine vascular response to hemorrhage during pregnancy with observations on therapy Obstet Gynecol *27* 549 1966

11 Greiss F C Jr Concepts on uterine blood flow *In* Obstetrics and Gynecology Annual *2* 53 1973

1 Hine I P Wood W G Mainwaring Burton R W Butler M J Irving M H & Booker B The adrenergic response to surgery involving cardiopulmonary bypass as measured by plasma and urinary catecholamine concentration Br J Anaesth *48* 355 1976

13 Høedt Rasmussen K Regional cerebral blood flow The intra arterial injection method MD-Thesis Copenhagen Munksgaard 1967

14 James F M Crawford J S Hopkinson R Davies P & Naiem H A comparison of general anesthesia and lumbar epidural analgesia for elective cesarean section Anesth Analg *56* 228 1977

15 Magno R Selstam U & Karlsson K Anesthesia for cesarean section II Effects of the induction delivery interval on the respiratory adaption of the newborn in elective cesarean section Acta Anaesthesiol Scand *19* 250 1975

16 Price H L & Helrich M Effects of cyclopropane diethyl ether nitrous oxide thiopental and hydrogen ion concentration on myocardial function of dog heart lung preparation J Phar Exp Therap *115* 206 1955

17 Rekonen A Luotola H Pitkänen M Kuikka J & Pyörälä T Measurement of intervillous and myometrial blood flow by an intravenous ^{133}Xe method Br J Obstet Gynaecol *83* 723 1976

18 Renaud R Bock A Chambron J Rosenthal C Raffi F Bidet R & Steinling M Etude simultanee des circulations placentaire myometriale et cervicale (Indium 133 et thermometrie anemnetique) 2 Effect du nicotinate de xantinol J Gynecol Obstet Biol Reprod (Paris) *5* 513 1976

19 Rosenfeld C R Barton M D & Meschia G Effects of epinephrine on distribution of blood flow in the pregnant ewe Am J Obstet Gynecol *124* 156 1976

20 Scott D B Lees M M Davie I T Slawson K B & Kerr M G Observations on cardiorespiratory function during caesarean section Br J Anaesth *41* 489 1969

21 Takki S Tammisto T Nikki P & Jäättelä A Effect of laryngoscopy and intubation on plasma catecholamine levels during intravenous induction of anaesthesia Br J Anaesth *44* 1323 1972

22 Wolkoff A S Bawden J W Flovers C E & McGee J A The effects of anesthesia on the newborn Am J Obstet Gynecol *93* 311 1965

Submitted for publication November 28 1977

Pentti Jouppila M D
Department of Obstetrics and Gynecology
University of Oulu
Oulu
Finland

ANNOUNCEMENT

IX WORLD CONGRESS OF GYNECOLOGY AND OBSTETRICS IN TOKYO

October 25–31, 1979

NEW TOUR ALTERNATIVES

Travel Arrangement No 1
Scandinavia – Tokyo – Scandinavia
23 10–3 11 1979
Takanawa Prince Hotel in Tokyo
The cost of this arrangement will be approximately Sw Crs 7 250

Travel Arrangement No 2
Scandinavia – Tokyo – China – Hong Kong – Delhi – Nepal – Scandinavia
23 10–13 11 1979
Keio Plaza Hotel in Tokyo
The cost of this arrangement will be approximately Sw Crs 11 990

Travel Arrangement No 3
Scandinavia – Tokyo – Bali – Sydney – Christchurch – Tahiti – San Francisco – Scandinavia
23 10–18 11 1979
Keio Plaza Hotel in Tokyo
Tour conductor Professor John Philip
The cost of this arrangement will be approximately Sw Crs 17 900

Detailed program can be requested from **World Tourist Travel Bureau** Bredgade 19 DK 1260 Copenhagen K Denmark Phone 01/151945 Gorm Pedersen/Niels Erik Christensen

These tours are planned by World Tourist Travel Bureau in Denmark in close cooperation with *Japan Travel Bureau* (the official agent of the congress) and *SAS – Globetrotter*





Acta Obstet Gynecol Scand 58 255—257 1979

COMPLICATIONS OF CERCLAGE

J G Aarnoudse and H J Huisjes

From the Department of Obstetrics and Gynecology University Hospital Groningen the Netherlands

Abstract The published results of cervical cerclage are almost invariably good and there is little mention of complications Forty per cent of 52 pregnancies with 38 early prophylactic and 14 late therapeutic operations ended after 260 days gestation In 73 per cent a viable infant was born

The most frequent complication was premature rupture of the membranes (12 cases) followed by slipping suture (7) and premature delivery (6) Intra uterine infection was fairly common The implications and possible causes of this high rate of complications are discussed

Cervical incompetence is an infrequent cause of fetal loss prevalence ranges from 0 5 to 5 cases per 1 000 pregnancies in the literature The etiology is not fully understood traumatic injury of the cervix appears to be the major cause but developmental abnormalities of the cervix and corpus uteri are associated in some instances with cervical incompetence (1 12) Some have suggested that an abnormal increase in uterine volume as seen in multiple pregnancy and polyhydramnios may result in cervical incompetence (2)

Clinically the classical course is dilation and effacement of the cervix without demonstrable uterine contractions and bulging of the membranes which rupture in most cases followed by a short and relatively painless labor and delivery of a fetus mostly born alive The diagnosis may be difficult only in those cases where the typical process has been completely observed is the diagnosis of cervical incompetence really proven A history of repeated fetal loss in the second trimester may raise suspicions of cervical incompetence but these data are usually subjective and often incomplete The reliability of a diagnosis in the non pregnant woman appears questionable (2 6)

The surgical treatment of cervical incompetence as introduced by Shirodkar (13) in 1955 gives good results as do the various modifications including the cerclage described by McDonald (5) in 1957 Effectivity is usually considered identical with an increase in the number of pregnancies resulting in viable infants after the operation Complications such as premature labor premature rupture of membranes and intra uterine infections are known but have received relatively little attention we therefore decided to analyse the results and complications of all cerclage operations performed from 1971 to 1976 in our Department

PATIENTS AND METHODS

In the five year period from 1971 5 278 women delivered in our department Fifty five cerclage operations were performed in 52 pregnancies of 40 patients These women had gone through 97 previous pregnancies resulting in 17 surviving children and 80 spontaneous abortions and premature deliveries 20 of which occurred prior to the 16th week

In 38 pregnancies the cerclage operation was performed because the obstetrical history raised the suspicion of cervical incompetence the criteria used were a history of fetal loss in the second trimester without signs of primary fetal death fetal abnormalities or placental insufficiency other maternal causes such as diabetes and infections were also excluded as far as possible In this group the operation was carried out between the 14th and 16th week of gestation except in two patients who had a cerclage before the onset of pregnancy because of recurrent cervical infection

The remaining 14 cerclage operations were performed on account of symptoms indicating a developing cervical incompetence during pregnancy in most cases the diagnosis was made after the patient developed the typical complaints of watery vaginal discharge and a feeling of pressure in the vagina the four cases of multiple pregnancy in this group (three twins and one triplet) could be diagnosed because vaginal examination in these pregnancies is a routine procedure after the 16th week of pregnancy The mean duration of pregnancy at the time of cervical suturing in the second group was 26 weeks

In six of the 40 patients previous injury to the cervix might have been responsible for the cervical incompetence (Table I) From 24 patients a hysterogram was available two showed a bicornuate and one an arcuate uterus Curettage revealed a bicornuate uterus in another patient

Operative technique After desinfection of vulva vagina and portio with a 0 0? per cent solution of chloorhexidine in water a double silk nr 5 purse string suture was inserted under general anesthesia round the cervix as high as possible The knot was not covered by cervical epithelium Postoperatively the patients were kept in bed for 24 hours

Table I *Possible causes of previous cervical injury in six patients*

- precipitate labour in a nulliparous woman the baby weighing 4 5 kg
- cervical laceration after vacuum extraction
- vacuum extraction through a rigid not fully dilated cervix
- first trimester termination (17th week) with dilation of the cervix
- severe post operative infection after caesarean section (2 cases)

and discharged 2-4 days after the operation If uterine contractions were demonstrable the patients were treated with ritodrine Except for a few with a very bad obstetrical history all patients were followed in the outpatient clinic at two-weekly intervals and in those without serious complications the suture was removed in the 38th week of pregnancy

Cervical suturing was judged completely successful if delivery took place after a gestation of 260 days or later in all cases with an earlier delivery the treatment was considered unsuccessful In the unsuccessful group we differentiated between cases of premature delivery with a surviving infant and those in which the baby died as a result of prematurity

RESULTS

Twenty one (40 per cent) of the 52 pregnancies ended after a gestation longer than 260 days In the remaining 31 cases (including three twins and one trip) the treatment was not successful according to our eria Seventeen children in the latter group sur d the neonatal period with a mean duration of regnancy of 33 5 weeks

The complications considered responsible for the failures were premature rupture of the membranes (12 cases) a slipping suture (7 cases) uterine infections (4 cases) and untreatable premature labor (6 cases) Two fetuses died intrauterinely and in another two cases no obvious cause for the failure could be demonstrated (Table II) In 10 patients intra uterine infections were made probable after delivery by positive cervical culture microscopic chorioamnionitis or maternal fever

The results of cervical cerclage in multiple pregnancies merit separate mention in two twin pregnancies and one triplet pregnancy cerclage was performed in the 29th the 33rd and the 25th week respectively In all three cases the membranes ruptured within a few weeks and labor started A third patient carrying twins presented at 22 weeks with a cervical dilation of 4 cm and cerclage was unsuccessful

DISCUSSION

The number of patients in our group with a history of possible traumatic injury of the cervix was relatively small in the literature the incidence of traumatic etiology varies widely Some authors report a high incidence of second trimester abortion and premature delivery after previous first trimester termination (10 14) Although it has been suggested that cervical incompetence is associated with a higher incidence of developmental abnormalities of the genital tract we did not find many of these abnormalities

If one considers the success rate of the operation as the percentage of pregnancies ending in the birth of one or more viable children we had a success rat of 73 per cent this is within the range of 37 to 80 per cent reported in the literature (3 7) However in our group one third of the surviving newborns was born prematurely Most workers do not report the prematurity rate Naver (7) found 27 per cent viable prematures and Nwosu (8) 29 per cent

Premature rupture of the membranes was the most frequent complication the etiology is not fully understood Perhaps a subclinical intra-cervical infection may result from the operation and affect the membranes another explanation might be a primary defect of the membranes as reported by Parry Jones en Priya (9) they found a significant decrease in the elasticity of those membranes which ruptured before labor irrespectively of the maturity of the pregnancy This would mean that the diagnosis of cervical incompetence was incorrect in those patients

Premature uterine contractions are a well known complication after cervical suturing the highest incidence is reported in the immediate postoperative period most probably as a result of cervical manipulation during operation However in our experience in most cases successful treatment with ritodrine was possible to avoid cervical injury it is important to re-

Table II *Complications diagnosed on admission of 31 unsuccessful cerclage operations*

Complication	Cases No
Premature ruptured membranes	12
Slipping suture (without demonstrable uterine contractions)	7
Untreatable premature uterine contractions	6
Intrauterine infection	4
Primary fetal death	2
Unknown	2

in two cases resuturing was possible

move the suture as soon as possible in those patients which do not respond to treatment Slipping off or cutting through of the suture is also seen without de monstrable uterine activity the most likely explana tion in these cases is too much tension on the suture resulting from the rapidly increasing uterine volume but one cannot always exclude the possibility of un observed uterine contractions Successful resuturing is possible in some cases

Intra uterine infection is difficult to prevent The suture is a corpus alienum in the cervical tissue in truding into the vaginal lumen uncovered by epitheli um a situation liable to entertain infection In fact in most cases profuse vaginal discharge is seen The cerclage operation according to Shirodkar has the ad vantage of covering the suture completely however most authors comparing the Shirodkar and the (more simple) McDonald procedure could not demonstrate any difference in complication rate and fetal outcome (7 11)

A special group are the patients with multiple preg nancies it has been suggested that abnormal increase in uterine volume may result in cervical incompe tence a phenomenon also observed in patients with polyhydramnios It still has to be proven whether a sutured cervix can offer satisfactory resistance in this situation

The number of intra uterine infections seen at de livery was considerable In some cases the cause of in fection was a preexisting cervical inflammation in most cases the most likely explanation is a long period of ruptured membranes If signs of intra uterine in fection were absent it was our policy in cases of in s fficient maturity to postpone delivery as long as p sible

The optimal time of operation is before the 20th week thereafter the success rate is lower because the indication for operation is nearly always an already developing cervical incompetence (7 11) We had the same experience the results from the operations be fore 20 weeks were slightly better

Conclusion Pregnancy outcome after a cerclage operation in patients with a diagnosis of cervical incom petence is clearly improved However the high num ber of complications after the procedure is disap pointing It is of course questionable whether the complications are a result of the operation but to an swer this question is indeed very difficult It is beyond doubt that our findings stress the importance of care ful selection for operation For this reason some have recommended clinical observation instead of a prophylactic cerclage in cases with a doubtful history of cervical incompetence only in cases of manifest in competence is the operation performed (8) However this method has the disadvantage of prolonged hospi talization Treatment of a preexisting cervical infec tion may reduce the number of complications and frequent inspection of the cervix after the operation is advisable to detect slipping off from the suture at an early stage when resuturing is still possible

REFERENCES

1 Asplund J The uterine cervix and isthmus under nor mal and path ological conditions Acta Radiol Supple mentum 91 1952

2 Barter R H Hsu I Erkenbeck R V & Pugsley L Q The prevention of prematurity in multiple preg nancy Am J Obstet Gynecol 91 787 1965

3 Baumgarten K Kritische Betrachtungeen zur Indika tion und Operationstechnik bei Zervixinsuffizienz Ge burtsh u Frauenheilk 25 260 1965

4 Bengtsson L Ph Cervical insufficiency Acta Obstet Gynecol Scand Suppl 1 9 1968

5 McDonald I A Suture of the cervix for inevitable miscarriage J Obstet Gynecol Brit Emp 64 346 1957

6 McDonald I A Incompetent cervix as a cause of re current abortion J Obstet Gynecol Brit Cwlth 70 105 1963

7 Naver E The incompetent cervix and its treatment in habitual abortion and premature labour Acta Obstet Gynecol Scand 47 314 1968

8 Nwosu U C Soffronoff E C & Bolton G C A new look at the etiology of cervical incompetence Int J Gynaecol Obstet 13 01 1975

9 Parry Jones E & Priya S A study of the elasticity and tension of fetal membranes and of the relation of the area of the gestational sac to the area of the uterine cavity Br J Obstet Gynaecol 83 05 1976

10 Richardson J A & Dixon G Effects of legal termi nation on subsequent pregnancy Br Med J 1 1303 1976

11 Robboy M S The management of cervical incompe tence Obstet Gynecol 41 108 1973

1 Roddick J W Buckingham J C & Danforth D N The muscular cervix A cause of incompetency in preg nancy Obstet Gynecol 17 567 1961

13 Shirodkar V N A new method of operative treatment for habitual abortions in the second trimester of preg nancy Antisepti 52 299 1955

14 Wright Ch S W Campbell S & Beazley J Second trimester abortion after vaginal termination of preg nancy Lancet I 1 77 1972

Subm tted f publicati n Novembe 14 1977

J C Aarnoud e
Department of Obstetrics and Gynecology
Uni e sity H sp tal Groningen
The N the l nd



Acta Obstet Gynecol Scand 58 259–263 1979

PREGNANCY COMPLICATIONS FOLLOWING CONIZATION OF THE UTERINE CERVIX (I)

Tom Weber and Erik Obel

From the Department of Obstetrics and Gynecology YA and YC University of Copenhagen Copenhagen Denmark

Abstract The literature on the course of pregnancies following conization of the uterine cervix has been studied It is demonstrated that an evaluation of the possible effect of conization upon subsequent pregnancy should be based upon a comparison of either pregnancies before and after conization or upon a comparison between pregnancies in women with a previous conization and in a control group of women without conization In both cases the possible influence of conization can be evaluated only if the patient material is described as regards age parity number of previous pregnancies smoking habits etc factors which may all influence the course of pregnancy None of the previous publications have described the patient material sufficiently and most studies have not tried to set up control groups

Due to these deficiencies we do not find it justified that conization leads to reduced fertility increased frequency of spontaneous abortion nor to increased perinatal mortality An increased prematurity rate may not be rejected however but this point has not been adequately evaluated in the previous papers

Since 1928 when Ryams (18) introduced conization of the cervix this procedure has been generally adopted For the first 30-35 years the operation was carried out mainly because of cervicitis (1 2 3 11 16 17) the last 15 20 years because of dysplasia or carcinoma in situ of the uterine cervix (4 5 6 7 8 9 10 12 13 14 15 19 20)

It is to be expected that the increasing use of screening for malignant diseases in the uterine cervix will result in an increased number of conizations being done on fertile women and that part of these women will become pregnant later on

Pregnancies following conization have first been described by Miller and Todd (16) in 1938 They concluded that conization should not be performed on fertile women Since then there has been a strong difference of opinion as to the possible negative effect upon subsequent pregnancies

In the light of previous publications on this subject we found it of interest to evaluate in which way the fertility and the course of pregnancy was influenced by conization

Two fundamentally different methods may be adopted to evaluate this problem You can either in a group of women with conization compare fertility and course of pregnancy before and after conization or you can compare a group of women with a previous conization with a control group of women without conization The advantage of the former method is that the patients themselves act as control group which guarantees the greatest parity between conizations and controls Fertility and course of pregnancy before and after conization do not compare uncritically however because after the conization some of the woman s characteristics are not the same as before the operation such as the woman is older than before the conization she may have developed other diseases than the one operated upon or been submitted to other gynecological operations her social status may have changed as well as her smoking habits or she may have changed partner Besides the rate of pregnancy complications is influenced by the number of previous pregnancies and this rate is higher after the conization than before Therefore in this type of studies these variables should be evaluated and adjustment be made accordingly In studies where women with a previous conization are compared with other women it is necessary to consider if only the first pregnancy following conization is examined or if all postconization pregnancies are evaluated as a whole The control group may be established at random or by matching The latter method makes the groups comparable as regards the matching criteria but it doues not preclude other differences from influencing the result So by matching as well as by a random selection of a control group further characteristics of the patients should be registered such as age number of previous pregnancies and their outcome socio-economic status medical diseases gynecologi



Table II *The number of spontaneous first trimester abortions and induced abortions in coni ed women*

Reference	Early spontaneous abortion (a)		Induced abortion (b)		Maximum rate of abortion in countries with liberal abortion legislation (c)	
	No	%	No	%	No	%
1 Bank 1960	3/ 42	7	8/42	19	3/34	9
2 Champion 1961	5/ 48	10				
3 Crossen 1949	19/ 95	20				
4 Fettig 1962	5/ 9	56				
5 Fettig 1963	5/ 15	33				
6 Huttmair 1967	2/ 6	33				
8 Kern 1967	8/ 38	21				
9 Kullander 1971	5/ 70	7	11/70	16	5/59	8
11 Lemberger 1962	7/105	7				
12 Litschgi 1974	5/ 14	36				
14 McLaren 1974	13/ 68	19				
15 McVicar 1968	30/177	17				
16 Miller 1938	3/ 15	20				
17 Retsch 1965	4/ 26	15				
19 Tornai 1970	2/ 78	3	56/78	71	2/22	9
20 Trnka 1968	1/ 93	1	45/93	48	1/48	2

(a) No of pontaneo abortions/No of p egnancies
(b) No of induced abortions/No of pregnancies
(c) No of spontaneous abort ons/No of pregnancies *less* No of induced abort ons
Country of orig n 1 and 19 Hungary 9 Sweden 20 Czechoslo akia

ticles without ectopic pregnancies have no indication of this factor and are thus not included in table III

Late abortion Late abortion is defined as a spontaneous abortion later than 12 weeks of gestation The calculation of the frequency of late abortions is based only upon pregnancies which had not ended within 13 weeks of gestation As mentioned above reservations should be made as regards the results stated in table IV as it is not clearly defined in all papers what the difference is between early and late abortion Table IV indicates that papers with more than 25 pregnancies consider the frequency of late abortion to be between and 11 per cent

P ematurity Prematurity is in the actual papers as a gesta o al age of less than or equal to 36 weeks of gestation or a birth weight below 2 501 grams At the bottom of table IV is indicated however that only about half the papers have stated how they define prematurity Table IV shows that in papers with more than 25 patients the prematurity rate varies between 1 and 17 per cent None of the papers mentioned states an increased rate of perinatal mortality following conization

Frequency of cesarean section As indications for cesarean section vary a great deal from department to department the section rates are diffi ult to compare Our attempt is indicated in table IV The frequencies range from 0 to 8 per cent which is a lower frequency of cesarean section than in many obstetrical departments today

DISCUSSION

The aim of the present paper was to evaluate if the relevant literature supports the theory that conization of the uterine cervix decreases the fertility and/or increases the risk of complications in a subsequent pregnancy

From a theoretical point of view conization may cause cervical insufficiency due to a shortening of the uterine cervix and/or damage of the uterine orificium Such a cervical insufficiency might increase the risk of late abortion and of premature delivery It is however difficult to imagine that conization could alter the fertility or increase the risk of early spontaneous abortion

As already indicated (table I) there is no certain evidence of reduced fertility following conization but the difference of opinion is very strong Thus Fettig (5) reports reduced fertility after conization Trnka (20) finds that fertility sometimes increases after coni

Table III *The number of ectopic pregnancies in coni ed women*

Reference	Rate of ectopic pregnancy (a)	
	No	%
2 Champion 1961	1/ 48	2 1
4 Fettig 1962	1/ 9	11 1
5 Fettig 1963	1/ 15	6 7
9 Kullander 1971	0/ 70	0 0
12 Litschgi 1974	0/ 14	0 0
14 McLaren 1974	1/ 68	1 5
15 McVicar 1968	1/177	0 6

(a) No of ectop c pregna ies/No of pregnancies

Table IV *The number of late abortions the frequency of prematurity and the number of Caesarean sections in conized women*

Reference	Late abortions (a)		Prematurity (b)		Rate of section ( )	
	No	%	No	%	No	%
1 Bank 1960			1/ 31	3		
2 Champion 1961			1/ 42	2		
3 Crossen 1949	5/ 71	7				
5 Fettig 1963	1/ 9	11	0/ 8	0		
7 Holzer 1972			22/130	17	8/130	6
8 Kern 1967	3/ 28	11	6/ 25	24	1/ 25	4
9 Kullander 1971	1/ 54	2	6/ 50	12		
11 Lemberger 1962			1/ 98	1	3/ 98	3
12 Litschgi 1974	0/ 9	0	1/ 9	11	0/ 9	0
13 McLaren 1967			2/ 32	6		
14 McLaren 1974	2/ 53	4	3/ 51	6	4/ 51	8
15 McVicar 1968	3/146	2	4/143	3	8/143	6
16 Miller 1936			4/ 12	33		
17 Retsch 1965	4/ 22	18	1/ 16	6		
19 Tornai 1970	1/ 20	5			1/ 19	5
20 Trnka 1968					0/ 47	0

(a) No of late abortions/No of pregnancies after 12 weeks of gestation
(b) No of premature deliveries/No of pregnancies after 7 weeks of gestation
(c) No of Caesarean sections/No of pregnancies after 27 weeks of gestation
Prematurity indicated as weight below 2500 g in reference 7 8 9 and 14 – indicated as gestational age less than 36 weeks in reference 2 15 and 17 – no further definition in reference 1 5 11 12 13 and 16

zation and for very special cases of infertility (cervicitis?) Recht (17) even recommends conization as the treatment of choice None of the papers mentioned has compared the fertility found with a control group and descriptive variables are not indicated in these articles the value of a comparison with a alled standard material is doubtful Another lem when evaluating fertility is a possible tenden to describe an originally unwanted pregnancy as wanted in cases when it is carried through This would increase the rate of conceptions in the groups of wanted pregnancy and thus result in an incorrect high fertility rate in the material

The abortion rates quoted in table II do not support the theory of increased risk of early spontaneous abortion following conization The high rate of first trimester abortions stated in a few articles may be explained by the fact that some of these abortions are performed illegally This statement may be supported by the fairly high rate of unwanted pregnancies following conization (table I) and also by the comparatively high rate of induced abortion in countries with a liberal abortion legislation As already indicated the frequency of early spontaneous abortions following conization is probably between 1 and 9 per cent This rate is only based on four papers with a total of 11 spontaneous abortions but seems to indicate that the risk of spontaneous abortion during the first trimester is not increased

The patient materials are too small to permit an evaluation of the frequency of late abortion with any degree of certainty A total of 20 (5 per cent) of 41? pregnancies recorded ended in a second trimester abortion This frequency does not seem to be surprisingly high but a further evaluation is not possible

The rate of prematurity depends on one hand on the patients background and on the other on the obstetrical service These factors may vary from article to article Possibly such variations may contribute to the diverging statements below Thus two comprehensive articles from 1971 and 1972 with 180 patients in all record a prematurity rate of 17 per cen (7) and 12 per cent (9) These results are balanced by two other big material (14 15) from 1968 and 1974 with a total of 194 patients These two articles record a frequency of 6 per cent If all papers with more than 25 patients are looked upon as a whole we find 40 premature deliveries (7 per cent) of 577 pregnancies in all The very diverging statements of prematurity may be due to the fact that the patient materials do not compare as regards descriptive variables but also different methods of conization especially the height of the cone biopsy may explain the diverging results

The papers mentioned only report two cases of application of cerclage (8 12) in conized women and

seven cases (2 7 14 15) of suspected cervical stenosis based upon the duration of labor and fibrosis of the uterine orifice This is eqivalent to 2 and 7 per thousand respectively of all pregnancies described These rates are very small and should be taken with great reservation as the indication for cerclage varies greatly from obstetrician to obstetrician and because the diagnosis of cervical stenosis is almost subjective

CONCLUSION

A survey of the relevant literature did not support the theory that fertility or the risk of early or late abortion is changed following conization However an increased risk of prematurity cannot be rejected The literature does not warrant any decisive conclusions as there are methodological sources of error in the studies published Especially the abscence of control groups damages the value of these studies

REFERENCES

1 Baradlai Bank E Die Wirkung der Zervix Konisation auf die Fertilität und auf die Gestationsvorgänge Gynaecologia *149* 26 1960
2 Champion P K & Thompson N J Effect of conization of the cervix on subsequent pregnancy Am J Obstet Gynecol *6* 1321 1951
3 Crossen R J Wide conization of cervix Am J Obstet Gynecol *57* 187 1949
4 Fettig O & Hillemanns H G Die Zervixkonisation Dtsch med Wsch *23* 1197 1962
5 Fettig O & Kühn C Konzeptionshäufigkeit Schwangerschafts und Geburtsverlauf nach Zervixkonisation Geburtsh Frauenheilk *23* 517 1963
6 Hittmair A Erfahrungen mit der Elektrokonisation der Portio Wien med Wschr *117* 855 1967
7 Holzer E Fertilität Schwangerschafts und Geburtsverlauf nach Konisation der Portio vaginalis uteri Geburtsh Frauenheilk *32* 950 1972
8 Kern G & Aslani A & Kern Bontke E & Gräfin zu Eulenburg H Folgen der Zervixkonisation Geburtsh Frauenheilk *27* 879 1967
9 Kullander S & Sjöberg N Treatment of carcinoma in situ of the cervix uteri by conization Acta Obstet Gynecol Scand *50* 153 1971
10 Kummert W Spätergebnisse nach diagnostischer und therapeuthischer Portiokonisation Zbl Gynäk *92* 1569 1970
11 Lemberger F Schwangerschaften nach Operationen der Portio Münch med Wschr *104* 1330 1962
12 Litschgi M & Benz J J Konisation und Fertilität Fortschr med *92* 1240 1974
13 M Laren H C Conservative management of cervical precancer J Obstet Gynaecol Brit Cwlth *74* 487 1967
14 M Laren H C Jordan J A & Glover M & Attwood M E Pregnancy after cone biopsy of the cervix J Obstet Gynaecol Brit Cwlth *81* 383 1974
15 McVicar J & Willocks J The effect of diathermy conization of the cervix on subsequent fertility pregnancy and delivery J Obstet Gynaecol Brit Cwlth *75* 355 1968
16 Miller N F & Todd O E Conization of the cervix Surg Gynec Obstet *67* 265 1938
17 Retsch H H & Wolff C Die therapeutische Elektrokonisation bei Frauen im fertilen Alter Geburtsh Frauenheilk *25* 253 1965
18 Ryams M N A new instrument for excision of the diseased endocervix with surgical diathermy N Y State J Med *28* 646 1928
19 Tornai I & Klacsmann L Fruchtbarkeitsproblem nach Kollumrehabilitierung Zbl Gynäk *92* 1499 1970
20 Trnka V & Skoda V & Novotna J Der Einfluss der Amputation und der Konisation der Portio vaginalis uteri auf die Fertilität und den Schwangerschaftsverlauf Geburtsh Frauenheilk *28* 1011 1968

Submitted for publication October 10 1977

Tom Weber M D
Department of Obstetrics and Gynecology YA
Rigshospitalet
Blegdamsvej 9
DK 2100 Copenhagen Ø
Denmark

Acta Obstet Gynecol Scand 58 265–270 1979

EVALUATION OF SMEARS OBTAINED BY CERVICAL SCRAPING AND AN ENDOCERVICAL SWAB IN THE DIAGNOSIS OF NEOPLASTIC DISEASE OF THE UTERINE CERVIX

Preben Johansen Erik Arffmann and Gorm Pallesen

From the Department of Pathology and the Department of Gynecology and Obstetrics Aalborg Hospital Section North Aalborg Denmark

Abstract A study of the supplementary value of an endocervical swab smear in addition to cervical scraping in the cytological diagnosis of cervical neoplasias is presented The two sampling techniques were applied to a population with a high prevalence of neoplastic cervical disease The endocervical swab smear was a useful adjunct in the detection of mild and moderate dysplasia and a combination of the two sampling methods decreased the false negative rate in the diagnosis of intraepithelial as well as invasive neoplasia In the sphere of specific cytological diagnosis cervical scraping was found to be the more accurate method for diagnosing severe dysplasia and carcinoma in situ while endocervical swab smears were more useful in diagnosing mild and moderate dysplasia Differences between the results obtained in our study and comparable studies are discussed It is concluded that the endocervical swab smear is a valuable adjunct to cervical scraping in the diagnosis of malignant cervical disease It should not however be used as the only sampling method as it produces a higher proportion of unsatisfactory smears and also because the severity of the epithelial lesion is more likely to be underestimated

A number of sampling techniques have been designed for the cytological detection of cervical neoplasia Studies on the diagnostic value of the various cellular samples obtained are however difficult to compare This is mainly due to differences in diagnostic nomenclature in the populations examined and in the way of expressing the diagnostic value of the sampling techniques involved A precise test of a diagnostic method in cytology is the false negative rate demonstrating the ability of the sampling procedure to pick up abnormal cells The false negative rate is best determined when the technique under study is applied to histologically proven cases Another important feature is the exact correlation of the specific cytological diagnosis with the final histological result There are few earlier studies that compare the false negative rates and the exact correlation with histology of different sampling methods in the cytodiagnosis of early cervical neoplasia Furthermore the results are to some extent conflicting

The screening of cellular samples consumes time and man power and in order to obtain maximum benefit from cervical cytology it is essential to know the diagnostic value of the various sampling techniques

The purpose of this study was to examine the diagnostic value of the endocervical swab specimen as an adjunct to the usual cervical scraping method in the diagnosis of neoplastic disease of the uterine cervix The test was applied to a population with a high prevalence of cervical neoplasias

MATERIAL AND METHODS

The study comprised 31? women seen consecutively during a nine months period in the Department of Gynecology and Obstetrics Aalborg Hospital having been referred because of an abnormal cervical smear obtained by the general practitioner or were patients followed up by cytology because of known intraepithelial neoplasia of the cervix A speculum examination was performed on each patient and a cervical scraping from the squamo-columnar junction with a dry Ayre spatula was taken Secondly an endocervical swab specimen was collected using a cotton tipped applicator The cotton tip premoistened with 0 9 per cent saline was introduced into the endocervical canal and rotated twice The two specimens were smeared on separate glass slides fixed in 96 per cent alcohol and stained ad modum Papanicolaou The two slides were examined independently

The cytological diagnoses were identical in nomenclature with the histological diagnoses i e no malignancy mild moderate or severe dysplasia carcinoma in situ and invasive carcinoma The diagnostic criteria were those described by Patten (3) When the smears revealed abnormal squamous cells not fulfilling the criteria for dysplasia carcinoma in situ or invasive carcinoma a diagnosis of atypical cells was made

Six per cent of the cervical scrapings and 11 per cent of the endocervical swab specimens were unsatisfactory In 168

Table I *Correlation between the cytological diagnosis determined from smears obtained by cervical scraping and the final histological diagnosis based on cervical curetting and/or biopsy cervical cone biopsy or hysterectomy specimen*

Final histological diagnosis	Cytological diagnosis (cervical scraping) No malignancy	Atypical cells	Mild moderate dysplasia	Severe dysplasia/ carcinoma in situ	Squamous cell carcinoma	Total
No malignancy	50	0	8	2	0	60
Mild moderate dysplasia	23	2	29	10	0	64
Severe dysplasia/ carcinoma in situ	5	0	11	33	1	50
Squamous cell carcinoma	1	0	0	1	6	8
Total	79	2	48	46	7	182

of the 312 patients both cellular samples were satisfactory and furthermore tissue specimens from the uterine cervix had been taken within 3 months of the cytological examination These 168 patients had a mean age of 33 years with a range from 19 to 62 years Nine per cent of the patients were over the age of 44 years

The tissue specimens consisted of punch biopsies and cervical curettings in 57 women a cone biopsy or a hysterectomy had been performed The punch biopsies were either quadrant biopsies or taken from areas not stained by the Schiller solution The cone biopsies were excised with a cold knife and the aim was to obtain a cone involving the endocervical canal almost to the internal os In 14 patients two sets of cytological and histological specimens were available *and therefore the whole study consisted of 182 paired* samples of specimens obtained from cervical scraping and endocervical swabs The tissue sections were reviewed by of us unbiassed and independently in order to obtain tency in diagnoses When disagreement occurred we ed the sections together to reach the final diagnosis

RESULTS

Tables I and II illustrate the correlation between the cytological diagnosis reached after examination of specimens obtained by cervical scraping and endocervical swabs respectively and the final histological diagnosis obtained from cervical curettings/biopsy cervical cone biopsy and/or hysterectomy specimens Mild and moderate dysplasia are grouped together as are severe dysplasia and carcinoma *in situ* This grouping stems from the fact that in our usual management of such patients cases of mild and moderate dysplasia are followed up at short intervals by cervical cytology while patients with severe dysplasia and carcinoma in situ will receive definitive treatment at the time of diagnosis Exact correlation with the histology was achieved in 118 of 182 cases (65 per cent) by the use of cervical scraping and in 115 of 182 cases (63 per cent) by the endocervical swab technique Cervical scraping correctly anticipated the histological diagnosis of mild moderate dysplasia in 29 of 64 cases (45 per cent) and the endocervical swab specimen in 42 of the 64 cases (66 per cent) In the severe dysplasia carcinoma in situ group exact correlation occurred *in 33 of 50 cases (66 per cent) using* cervical scraping and in 23 of 50 cases (46 per cent) by the endocervical swab technique Invasive squamous cell

Table II *Correlation between the cytological diagnosis based on the endocervical swab smears and the final histological diagnosis based on cervical curettings and/or biopsy cervical cone biopsy or hysterectomy specimen*

Final histological diagnosis	Cytological diagnosis (endocervical swab) No malignancy	Atypical cells	Mild moderate dysplasia	Severe dysplasia/ carcinoma in situ	Squamous cell carcinoma	Total
No malignancy	46	1	9	4	0	60
Mild moderate dysplasia	16	0	42	6	0	64
Severe dysplasia/ *carcinoma in situ*	7	0	20	23	0	50
Squamous cell carcinoma	0	0	1	3	4	8
Total	69	1	72	36	4	182

Table III Correlation between the final cytological diagnosis determined from a combination of the results of cervical scraping and endocervical swab smears and the final histological diagnosis based on cervical curettings and/or biopsy cervical cone biopsy or hysterectomy specimen

Final histological diagnosis	Final cytological diagnosis (cervical scraping and endocervical swab)					
	No malig nancy	Atypical cells	Mild moderate dysplasia	Severe dysplasia/ carcinoma in situ	Squamous cell carcinoma	Total
No malignancy	43	0	12	5	0	60
Mild moderate dysplasia	8	1	42	13	0	64
Severe dysplasia/ carcinoma in situ	3	0	11	35	1	50
Squamous cell carcinoma	0	0	1	1	6	8
Total	54	1	66	54	7	182

carcinoma was specifically diagnosed by cervical scraping in 6 of 8 cases while the positive finding in the endocervical swab specimen was underestimated in 4 cases

The combination of cervical scraping and endocervical swab technique resulted in an exact correlation with histology in 126 of the 182 cases (69 per cent) (*Table III*) *By this combined method mild moderate* dysplasia was diagnosed cytologically in 42 of 64 cases (66 per cent) and severe dysplasia carcinoma in situ in 35 of 50 cases (70 per cent) A cytological diagnosis of squamous cell carcinoma was made in 6 of 8 histologically proven cases by a cervical scraping alone but by the combined method the false negative was eliminated

Tables IV and V specify the false negative rates for cervical scraping and endocervical swab techniques also a combination of the two methods in cases of mild moderate dysplasia and of severe dysplasia carcinoma in situ Using the cervical scraping method 36 per cent of patients with mild moderate dysplasia remained undetected with the endocervical swab *technique this rate was 25 per cent When the two* methods were combined 13 per cent of these cases were missed In patients with severe dysplasia-carcinoma in situ the false negative rates occurring after examination of the material obtained by cervical scraping and endocervical swabs were 10 per cent and 14 per cent respectively and this rate was reduced to 6 per cent when the two methods were combined False positive results were obtained in 10 patients with cervical scraping and in 14 patients using the endocervical swab technique these showed atypical cells or cells indicating dysplasia or carcinoma in situ but histological examination of the tissue specimens revealed no malignancy (Tables I and II)

Tables VI VII and VIII illustrate the correlation between the cytological and the histological diagnoses in 57 patients in whom the tissue specimen obtained was either a cervical cone biopsy or the whole uterus In these patients all abnormal epithelium had been removed as the presence of neoplastic epithelium in the proximal or distal resection edge of the cone biopsy had further prompted hysterectomy As can be seen from the tables there were no false positive cytological diagnoses of neoplasia in these 57 cases This part of the study is dominated by patients with severe dysplasia carcinoma in situ namely 45 of the 57 cases Exact correlation with histology was seen in 29 cases (51 per cent) using the endocervical swab technique compared with 35 cases (61 per cent) when a cervical scrape was taken Combining the two techniques increased the accuracy of cytological diagnosis to 40 of the 57 cases (70 per cent)

DISCUSSION

The diagnostic value of gynecological cellular samples *in the detection of cervical neoplasias depends* upon the site from which the smears are taken It has

Table IV *False negative rates for smears obtained by cervical scraping an endocervical swab and a combination of the two techniques in the mild moderate dysplasia group*

Cell collection technique	False negative rate %
Cervical scraping	36
Endocervical swab	25
Cervical scraping and endocervical swab	13

Table V *False negative rates for smears obtained by cervical scraping an endocervical swab and a combination of the two techniques in the severe dysplasia carcinoma in situ group*

Cell collection technique	False negative rate %
Cervical scraping	10
Endocervical swab	14
Cervical scraping and endocervical swab	6

long been recognized that smears prepared from the vaginal pool are inadequate Wied (6) counted the number of abnormal cells in vaginal pool smears cervical scrapings and endocervical swab specimens from patients with known neoplastic disease of the cervix and found significantly lower values for the vaginal pool material Furthermore using the vaginal pool smear 11 of 50 patients with early invasive cancer and carcinoma in situ were undetected

The main object of our study was to examine the supplementary value of the endocervical swab smear in gynecological cytology when the routine procedure is examination of the smear obtained by cervical scraping Tables I II and III show that correlation h histology as to the specific diagnosis was present per cent and 65 per cent of the cases by use of al scraping and endocervical swab techniques pectively These summary percentages conceal however a significant difference in the ability to diagnose the various degrees of neoplasia The cervical scraping technique enabled us to correctly diagnose severe dysplasia carcinoma in situ in 66 per cent of the cases but only 45 per cent of mild moderate dysplasias In the latter category the false negative rate was as high as 36 per cent The endocervical swab specimen however resulted in the diagnosis of 66 per cent of the mild moderate dysplasias while exact correlation with histology in the severe dysplasia-carcinoma in situ group was present in only 46 per cent of the cases This difference was confirmed and further emphasized by analysis of the results based on cervical cone biopsies or hysterectomy specimens a positive correlation with the subsequent histology was found in 61 per cent of smears obtained by cervical scraping and 51 per cent by endocervical swabbing

Comparable results for dysplasia were obtained by Richart and Vaillant (4) who used external os aspiration before cervical scraping and had 17 per cent false negatives for endocervical aspiration in 176 cases of cytologically presumptive dysplasia as against 28 per cent false negatives by cervical scraping In contrast Shingleton *et al* (5) using endocervical aspiration or swabbing combined with cervical scraping found a false negative rate of 41 per cent for endocervical smears in mild moderate dysplasia and only 24 per cent false negatives for smears obtained by cervical scraping The endocervical swab technique in the latter study differed from the one we used by the use of dry cotton tipped applicators which may be inferior in ability to pick up cells

Nieburgs (2) emphasized the importance of the order in which the samples are taken He found that the first smear produced the lowest false negative rate because it utilized the cervical mucus plug which usually carries a large number of abnormal cells In our study the cervical scraping was taken first yet the endocervical swab smear was superior for detecting mild moderate dysplasia and the smear from cervical scraping revealed more cases of severe dysplasia-carcinoma in situ Richart & Vaillant (4) found the endocervical os aspirate taken before the cervical scraping

Table VI *Correlation between the cytological diagnosis determined from smears obtained by cervical scraping and the histological diagnosis based on cervical cone biopsy or hysterectomy specimen*

Final histological diagnosis	Cytological diagnosis (cervical scraping)					
	No malignancy	Atypical cells	Mild moderate dysplasia	Severe dysplasia/ carcinoma in situ	Squamous cell carcinoma	Total
No malignancy	2	0	0	0	0	[illegible]
Mild moderate dysplasia	1	0	1	3	0	5
Severe dysplasia/ carcinoma in situ	7	0	8	29	1	45
Squamous cell carcinoma	1	0	0	1	3	5
Total	11	0	9	33	4	57

Table VII *Correlation between the cytological diagnosis determined from smears obtained by an endocervical swab and the histological diagnosis based on cervical cone biopsy or hysterectomy specimen*

Final histological diagnosis	Cytological diagnosis (endocervical swab)					
	No malignancy	Atypical cells	Mild moderate dysplasia	Severe dysplasia/ carcinoma in situ	Squamous cell carcinoma	Total
No malignancy	2	0	0	0	0	2
Mild moderate dysplasia	0	0	4	1	0	5
Severe dysplasia/ carcinoma in situ	8	0	15	22	0	45
Squamous cell carcinoma	0	0	1	3	1	5
Total	10	0	20	26	1	57

to be the more accurate in the detection of dysplasia and carcinoma in situ while Shingleton *et al* (5) using the same order of smear taking found a remarkably higher false negative rate for the endocervical material when compared with that obtained by cervical scraping These observations indicate that variables other than the order of smear taking significantly influence the accuracy of cytological diagnosis

The comparing of different studies may be invalidated by the varying techniques used for obtaining the endocervical material Shingleton *et al* (5) however used endocervical swabbing in addition to aspiration and found the two smears equally accurate in the detection of neoplastic lesions of the endocervix

In our study a combination of the techniques of cervical scraping and endocervical swabs resulted in a reduction of the false negative rate especially in the mild moderate dysplasia category and also in the severe dysplasia-carcinoma in situ group This agrees with the observation of Richart and Vaillant (4) but Anderson and Gunn (1) in their study of carcinoma in situ and invasive carcinoma found no enhancement of the cytodiagnostic accuracy when smears from cervical scraping were supplemented by those obtained by endocervical swabs Shingleton *et al* (5) reached the same conclusion and pointed out that in only 2 9 per cent of the patients did the endocervical smear detect a lesion missed by cervical scraping Wied (6) who studied 50 cases of early invasive cancer including carcinoma in situ found significantly more abnormal cells in the endocervical swab specimen than in the cervical scraping This is in agreement with modern concepts of the topography of cervical carcinogenesis which localizes the highest degree of precancerous lesion more proximally in the endocervical canal

The decrease we found in the false negative rate using endocervical swabbing as an adjunct to cervical scraping may be due to either the fact that with this method more cells are available for assessment or because the endocervical swab smear picks up cases which have involvement of the anatomical endocervi

Table VIII *Correlation between the final cytological diagnosis determined from a combination of the results obtained by cervical scraping and an endocervical swab and the histological diagnosis based on cervical cone biopsy or hysterectomy specimen*

Final histological diagnosis	Final cytological diagnosis (cervical scraping and endocervical swab)					
	No malignancy	Atypical cells	Mild moderate dysplasia	Severe dysplasia/ carcinoma in situ	Squamous cell carcinoma	Total
No malignancy	2	0	0	0	0	2
Mild moderate dysplasia	0	0		3	0	5
Severe dysplasia/ carcinoma in situ	4	0	8	32	1	45
Squamous cell carcinoma	0	0	1	0	4	5
Total	6	0	11	35	5	57

cal canal alone In our study we made no attempt to correlate the diagnosis based on the endocervical sample with neoplastic involvement of the anatomical endocervical canal Due to cervical eversion common in women of childbearing age which comprised the majority of our patients we found it difficult to define the endocervical canal in histological sections Shingleton *et al* (5) found no clear correlation between positive and negative findings in endocervical smears and endocervical curettings It seems more likely that the sampling of a larger amount of cells reduces the risk of missing a positive case Mild and moderate dysplasia often involve only a small area of the cervix and are consequently more easily missed when only one smear is taken and it is especially in this group that the endocervical swab specimen provides the greatest aid to increasing the cytological diagnostic accuracy

The false positive rate is dependent upon the accuracy of the evaluation of the cytological smears We had no false positives in the 57 patients in whom cone biopsy or hysterectomy was performed The 10 false positive results from smears of cervical scrapings and the 14 false positive endocervical swab specimens seen in Tables I and II occurred only in those cases in which cytological findings were compared with histological diagnoses from cervical curettings and biopsies The cervical biopsies in our material were either quadrant biopsies or taken from areas not stained by ller s solution and some false negative biopsies herefore to be expected

e predictive value of the cytological diagnosis of vere dysplasia carcinoma in situ is of some importance In our management of patients cone biopsy may be performed on the basis of this cytological diagnosis even if cervical biopsies and curettings are negative or show a minor degree of intraepithelial neoplasia Tables VI VIII show that the reliability of cytological diagnosis is about equal for smears obtained by cervical scraping by endocervical swab and also a combination of the two methods

We conclude from our study that the endocervical swab smear contributes towards the detection of mild and moderate dysplasia and in this particular group is superior to the smear obtained from cervical scraping In severe dysplasia and carcinoma in situ cervical scraping however reveals more cases Both in mild moderate dysplasia and in severe dysplasia-carcinoma in situ a combination of the two methods enhances the diagnostic value of cytology by reducing the false negative rate The endocervical swab technique should however not be used as the only method because it results in a higher proportion of unsatisfactory smears and also an underestimation of the severity of the epithelial lesion

REFERENCES

1 *Anderson W A D & Gunn S A* The efficacy of a single cytology smear in the detection of cancer of the cervix Cancer Journal for Clinicians *13* 9? 1963
2 Nieburgs H E A comparative study of different techniques for the diagnosis of cervical carcinoma Am J Obstet Gynecol 72 511 1956
3 Patten S F Diagnostic cytology of the uterine cervix Monographs in Clinical Cytology Vol 3 S Karger Basel and New York 1969
4 Richart R M & Vaillant H W Influence of cell collection techniques upon cytological diagnosis Cancer *18* 1474 1965
5 Shingleton H M Gore H Straughn J M & Littleton H J The contribution of endocervical smears to cervical cancer detection Acta Cytol *19* 261 1975
6 Wied L G Importance of the site from which vaginal cytologic smears are taken Am J Clin Pathol *25* 4.. 1955

Submitted for publication November 10 1977

Preben Johansen M D
Department of Pathology
Aalborg Hospital
Section North
Aalborg
Denmark

Acta Obstet Gynecol Scand 58 271 – 274 1979

THE CRYOSURGICAL TREATMENT OF INTRAEPITHELIAL NEOPLASIA

Helen Marie Henriksen

From the Radium Centre Copenhagen Denmark

Abstract At the Finseninstituttet and the Radium Centre in Copenhagen from 1971 1975 inclusive cryosurgery was carried out altogether 59 times on 57 patients Only 8 patients showed histopathological changes in the biopsies sufficient to indicate conization

Hysterectomy was carried out on 8 patients In 7 of these the removed uteri showed either no malignant changes or changes of a lesser degree of malignancy than those which had indicated cryotherapy Invasive growth was discovered only in 1 patient who later underwent a total hysterectomy by the Wertheim method A biopsy on 1 patient with carcinoma in situ suspected invasive growth was treated with radium

The systematic use of vaginal cytology among younger gynecological patients has resulted in a sharp increase in diagnosed cases of intraepithelial neoplasia (1) Conization used to be the most common method of treatment both therapeutically and diagnostically However the post operative bleeding and/or cervical stenosis as well as complications associated with subsequent pregnancy (e g increased abortion rate abruptio placentae) that followed this operation resulted in the introduction by Crisp and Kauffmann of cryosurgery as a treatment for intraepithelial neoplasia in younger women who wished to retain their fertility (3 4 5) This method demands however a reliable histopathological diagnosis prior to treatment as well as an adequate follow up over a number of years following cryosurgery The purpose of this publication is to provide a survey of the results of 57 treated women with a varying degree of intraepithelial neoplasia over a 5 year period

MATERIAL AND METHODS

The material comprised 57 consecutive patients with a varying degree of dysplasia or carcinoma in situ Fig 1 shows the age distribution together with the treatment diagnosis arranged in decades 59 6 per cent of the patients were between 20 and 40 years of age and 84 2 per cent between 20 and 50 years of age Twentynine of the patients were treated for carcinoma in situ Fig 1 shows in addition that carcinoma in situ was the most frequent pretreatment diagnosis among the younger patients

About the age of 40 the squamous-epithelial junction is visible at the external os and since it is this same group of patients that desires continued fertility cryosurgery is used after the age of 40 only in those cases where other forms of treatment are counter indicated Altogether 59 treatments were undertaken 2 of the patients being treated twice Thirty of the subjects were treated as outpatients in the remaining 27 cases treatment was carried out during the hospitalization that commenced with the diagnostic curettage and/or biopsy

Therapeutic technique All the patients were treated without anaesthesia A cervical probe was applied to the external os its tip extending into the endocervical canal The probe temperature was about −72 C and freezing was carried out until a 4 mm border of frozen tissue had been achieved around the probe tip

In nearly all cases the freezing time was 4 min whereafter treatment was finished Only a few patients underwent the double freeze technique i e freezing followed by defrosting and refreezing All the patients were followed up as outpatients the first time 4 weeks after cryosurgery and then 8 weeks later A cytological smear was taken at this visit and then every 6 months If the cytology proved to be persistently abnormal the patient was readmitted for curettage of both the cervical canal and the corpus uteri and for cervical biopsies The results of these determined the patient s subsequent treatment All the patients were followed up for at least 2 years some for 6 – 7 years

RESULTS

Only 2 out of 12 patients who were treated for *mild to moderate dysplasia* demonstrated suspect cells at any one follow up during the period of observation In one case biopsy revealed nothing abnormal in the other moderate to severe dysplasia In both cases the subsequent cytology was normal The period of observation was 2 6½ years

16 patients with *moderate to severe dysplasia* underwent cryosurgery 18 times 2 of them being treated twice on account of persistent dysplasia The subsequent cytology was normal Three patients later underwent conization 4 times 1 of them because of persistent dysplasia 2 of them because of signs point

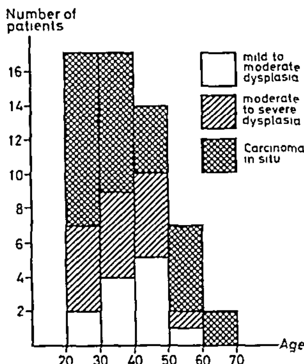


Fig 1 Age distribution and treatment diagnosis within the separate decades

ing to carcinoma in situ One of these subsequently underwent a hysterectomy the histological report showed no intraepithelial neoplasia Because of persistent tumor cells in the cervical secretion one patient in this group underwent curettage of both the cervical canal and the corpus uteri and a cervical biopsy which revealed endocervical cancer Without previous conization a total hysterectomy was then performed according to Wertheim s method The histological report showed invasive carcinoma of uterus The period of observation was 2½ – 7 years

In 5 of 29 patients treated by cryosurgery for *carcinoma in situ* biopsies later revealed a recurrence Subsequent conization revealed carcinoma in situ in 3 of the patients dysplasia in 1 patient and nothing abnormal in the other Histological reports on the removed uteri showed no malignant changes in 2 patients mild dysplasia in 1 patient and severe dysplasia in 1 patient 1½ years after cryotherapy biopsies revealed carcinoma in situ in 1 patient with suspected invasive growth the patient was treated twice with radium and since then cytology has been normal Conization has thus been carried out 9 times on 8 patients (Table I) Histological investigation of only two of the cases revealed more progress than in those that had indicated cryotherapy Table I also gives the time intervals between cryotherapy and subsequent conization

Table II shows that the uterus was removed in 8 cases 5 of which revealed no histopathological changes 2 showed dysplasia and 1 changes pointing to invasive cancer *Table II also shows the time intervals* between cryotherapy and conization between conization and hysterectomy and between cryosurgery and hysterectomy (conization has not been carried out in 2 patients)

Complications

In connection with the operation no patient suffered an increase in body temperature appreciable pain necrosis or bleeding sufficient to indicate blood transfusion but all patients had a watery vaginal discharge which ceased spontaneously after about 14 days Parametritis or salpingitis was not observed

Pregnancy following cryosurgery

Following a period of treatment 9 patients became pregnant In 3 cases an abortion was induced and 1 patient had spontaneous abortion Of the 6 full term pregnancies 4 patients were delivered vaginally and 2 by cesarean section on account of umbilical cord complications praeclampsia and age respectively neither of them causes that are relevant to cryosurgery

DISCUSSION

In the past decade the development of precision apparatus has led to new and improved applications for cryosurgery We are now able to procure an accurate and wellcontrolled cryonecrosis of the tissues so that this method of treatment may be used in many specialized fields such as neurosurgery opthalmology

Table I *Cases treated with cryosurgery and subsequent conization Histopathologic findings in biopsies and cone specimens*

Cryosurgery	Conization		Interval
Pretreatment biopsy	Preoperative biopsy	Cone specimen	cryo-cone (months)
CIS	CIS	CIS	4
CIS	CIS	mod/sev dyspl	3
CIS	CIS	CIS	43
CIS	CIS	CIS	77
CIS	CIS	no finding	4
mod/sev dyspl	CIS	CIS	19
mod/sev dyspl	mod/sev dyspl	no finding	17
mod/sev dyspl	CIS	CIS	3
same pt later	CIS	mod dyspl	

Table II *Cases treated with hysterectomy Histopathologic findings in biopsies and in hysterectomy specimens*

Cryosurgery	Hysterectomy		Interval (months)		
Pretreatment biopsy	Pretreatment biopsy or cone	Operative specimen	cryo-cone	cone hyst	cryo-hyst
CIS	CIS (+c)	mild dyspl	4	22	
CIS	mod/sev dyspl (+c)	epithelial hyperplasia	2	8	
CIS	CIS (+c)	epithelial hyperplasia	43	2	
CIS	CIS (+c)	sev dyspl	27	16	
mod/sev dyspl	CIS (+c)	no histopathol changes	19	0	
sev dyspl	cerv chron (+c)	no histopathol changes			20
sev dyspl	tumor cells (+c)	invasive carcinoma			15
CIS	CIS (+c)	no histopathol changes		10	

dermatology and gynecology

Crisp published a report in 1972 on 220 gynecological patients of whom 123 were treated by cryosurgery for dysplasia In 8 patients (6 5 per cent) dysplasia persisted but repeated cryosurgery gave good results (4) Similarly Townsend demonstrated recurrences in 6 out of 76 patients (7 9 per cent) and Kaufmann in 16 of 179 (8 9 per cent) (7 5) The above reports do not however say precisely when the recurrences ocurred or specify the length of the period of observation In the material under discussion we noted a recurrence in 1 out of 12 patients (8 per cent) with mild to moderate dysplasia 1½ years after cryosurgery Subsequent follow up revealed nothing abnormal Among 16 patients with severe dysplasia cryosurgery on 3 patients was supplemented with conization whereafter the vaginal cytology became normal One patient demonstrated invasive cancer (6 3 per cent) The somewhat varying results in the reports may be due to the different size of the patient material as well as the different length of the period of observation

Thirtynine patients with carcinoma in situ were treated by Crisp with cryosurgery (4) Only 1 patient (2 6 per cent) suffered minimal dysplasia following prolonged gonorrheal vaginitis Townsend s material consisted of 19 patients with carcinoma in situ of whom 10 5 per cent displayed persistent changes (7) Similarly 2 out of 11 patients (18 2 per cent) treated by Kaufmann revealed carcinoma in situ and 2 patients who underwent cryosurgery for carcinoma in situ subsequently manifested severe dysplasia (5) Stakemann and Nielsen s publication reveals that in 9 out of 11 patients who underwent cryosurgery for carcinoma in situ the uterus removed at hysterectomy showed a recurrence but the period of observation was only 4-10 week (6) Only in 3 of the 29 patients (10 3 per cent) under discussion here who later underwent conization has carcinoma in situ been found Histological examination of the uteri removed by hysterectomy revealed no changes however so we may conclude that all the patients in this group are cured A seemingly better result with these patients compared with the above mentioned authors may possibly be due to a closer follow up and a longer period of observation

With the exception of vaginal discharge which in nearly all the patients under discussion lasted for about 2 weeks there were no complications Crisp has described almost the same lack of complications whereas Townsend found severe vaginal discharge in all of his 95 patients spotting in 55 per cent flushing reaction in 10 per cent and severe pain in conjunction with the operation in 1 per cent (4 7)

Many authors would seem to prefer cryosurgery when treating cervical dysplasia and carcinoma in situ in women who wish to preserve their uterine function (2 3) In Crisp s publication among 123 patients with dysplasia 9 became pregnant of whom 8 were delivered vaginally at term and 1 had an abortion (4) Among 38 patients with carcinoma in situ 4 became pregnant following cryosurgery and all the pregnancies were uncomplicated Forty out of the 302 patients treated by Townsend Ostergard and Lidkrisk became pregnant 34 were delivered vaginally and in none was cervical insufficiency demonstrated (8) However in the above mentioned reports as well as in the material under discussion in which 9 patients conceived and 6 were delivered at term there was no history of undesired infertility use of

anticonception or the result of a possible hysterosalpingography so the information about the number of pregnancies is not conclusive for the patient s fertility following cryosurgery

The negative side of cryosurgery lies in the lack of histological investigation of the removed tissues But unlike conization as a method for treating intraepithelial neoplasia cryosurgery is painless thus rendering anesthesia unnecessary the loss of blood in minimal and not least this method of treatment saves both time and money for patient and hospital alike since the patients may be treated as outpatients

REFERENCES

1 Creasman W T & Rutledge F Carcinoma in situ of the cervix Obstet Gynecol 39 373 197?

2 Creasman W T Weed J C Curry S L Johnston W W & Parker R T Efficacy of cryosurgical treatment of severe cervical intraepithelial neoplasia Obstet Gynecol 41 501 1973

3 Crisp W E Smith M S Asadourian L A & Warrenburg C B Cryo surgical treatment of premalignant disease of the uterine cervix Amer J Obst Gynecol 107 737 1970

4 Crisp W E Cryosurgical treatment of neoplasia of the uterine cervix Obstet Gynecol 39 495 1972

5 Kaufmann R H Strama Th Norton P K & Conner J S Cryosurgical treatment of cervical intraepithelial neoplasia Obstet Gynecol 42 881 1973

6 Nielsen N C & Stakemann G Cryosurgery for carcinoma in situ of cervix Lancet 627 ii 1973

7 Townsend D E & Østergaard D R Cryocauterization for preinvasive cervical neoplasia J Reprod Med 6 171 1971

8 Townsend D E Østergaard D R & Licktish G M Cryosurgery for benign disease of the cervix J Obstet Gynaecol Br Comm 78 667 1971

Submitted for publication August 8 1977

Helen Marie Henriksen
Nordens Plads 4 28 etage lejl 5
DK 2500 Valby
Denmark

Acta Obstet Cynecol Scand 58 275 – 278 1979

METHODS FOR EVALUATING THE INTRAUTERINE LOCATION OF CARCINOMA

P Liukko M Grönroos R Punnonen and P Kilkku

From the Department of Obstetrics and Gynecology University Central Hospital Turku Finland

Abstract The intrauterine location of endometrial carcinoma was investigated with curettage hysterography and hysteroscopy in 83 patients These three methods are complementary Curettage provides important information about the differentiation of the tumor Hysterography is suitable especially for elucidating the anatomy of the cervical canal and uterine cavity Direct examination by hysteroscopy gives a reliable picture when defining the boundary between stages I and II

In addition to the patient s general condition age and extragenital diseases the following factors affect the treatment and prognosis of endometrial carcinoma the size of the uterine cavity the sound measurement the depth of the neoplasm in the myometrium the grade of malignancy and the anatomic spread Especially decisive factors for the route and rate of spread of the tumor are its point of origin and intrauterine invasion All these factors are moreover often interdependent

A lesion located in the fundus is known to spread more slowly on average than processes in th isthmus and endocervix Kottmeier Parsons and Cesare advised already in 1959 more radical operative treatment for endometrial carcinoma of the lower segments (6 9) Tumors of the fundus spread via the subovarian plexus and the ligamentum infundibulo pelvicum cranially into the para aortal lymph nodes and sometimes along the ligamentum rotundum into the inguinal nodes Isthmic processes on the other hand usually spread in the manner of cervical carcinoma and reach the interiliacal nodes

Establishing the intrauterine location of the tumor is important for the planning of therapy and for following the international clinical staging Curettage hysterography and hysteroscopy are the primary diagnostic methods (2 3 4 5) We have been using these techniques in parallell since 1975 Their clinical use and diagnostic accuracy are evaluated here

MATERIAL AND METHODS

The material comprised 83 patients with carcinoma of the uterine body treated at the University Central Hospital Turku in 1976-1977 All of these patients underwent curettage 49 had hysterography and 61 hysteroscopy The mean age of patients was 64 5 years (range 39 88 years)

Fractionated curettage has a long-established role both in carcinoma diagnostics and in the determination of the tumor s stage However the finding may vary in repeated curettages Cervical scraping may involve contamination from the corpus alternatively carcinoma tissue may move to the corpus in connection with dilatation False negative results have been as frequent as 30 per cent in some materials (8 11) It may also happen that carcinoma tissue is no longer found at new curettage in previously verified cases of carcinoma the figure aries between 1 3 and 10 per cent in the literature (11) A small carcinomatous area for instance at the tip of a polyp may be totally eradicated or equally well may evade the curette when it is behind e g a myoma defor

Table I *Clinical stage evaluation by primary and secondary curettage*

		Secondary curettage					
Primary curettage		Clin st I	Clin st II	Susp st II	Clin st III IV	No Ca	No curettage
Clin st I	38	13	4	9	—	9	3
Clin st II	15	3	9	[illegible]	—	—	1
Susp st II	13	7	2	2	—	1	1
Total	66	23	15	13	—	10	5

Table II *Correlation between primary curettage and the final clinical stage*

Primary curettage		Final clinical stage St I	St II	St III IV
Clin st I	38	32	5	1
Clin st II	15	1	13	1
Suspect II	13	8	5	—
No fract	17	14	2	1
Total	83	55	2	3

mation In the material in which fractionated curettage was checked by means of microscopic specimens taken at hysterectomy without preceding radiotherapy spread to the cervical region was established in 12 16 per cent of the changes classified as being of stage I (5) We performed the curettage as a fractionated procedure in which the cervical and corpus scraping were treated separately The scraping from the cervix was taken prior to dilatation

Hysterography has also been used to establish the spread of carcinoma of the uterine body Especially the Swedish authors (5 8) recommend it as a supplementary examination However it is difficult to distinguish a malignant tumor reliably from a benign neoplasm Moreover the patients have often undergone several curettages before the hysterography Hysterographies may alter the mural configuration especially in the region of the cervix and the isthmus Hysterography has been criticised in the literature chiefly because of the migration of corpus carcinoma cells via the bes into the abdominal cavity In substantial materials ever this has not proved to be of importance for the nosis (1) All the same we tried to avoid flow into the e by using a low pressure from 40 to 100 mmHg Perjodal H Viskös^R (35 per cent) (Pharmacin) was the contrast medium used The instrumentation was a Schulze hysterosalpingography instrument Because of the low pressure flow into the tube occurred in only 20 per cent of our series and intravasation which is reported to be a typical occurrence in carcinoma patients was encountered in 2 per cent (10)

We have also used *hysteroscopy* with Stortz s optics for direct examination of the uterine cavity and the cervix We used dextran (40 per cent) which is highly viscous a d gives good optical conditions for the examination In addition slightly greater dilatation than is required for the hysteroscope prevents the flow of dextran into the tube

RESULTS

Table I presents the comparison between the primary and the secondary curettage the latter being performed in conjuction with the initial radiation therapy There were 11 cases in which the previously verified carcinoma was no longer encountered at secondary curettage and in one case the lesion was now interpreted as carcinoma in situ No secondary curettage was performed on the patients in the last column Table II shows the ratio between the final staging grouping which was performed as a comprise between all the permissible studies and primary curettage Five of 38 cases of stage I grouping changed to stage II whereas the final staging was lower by one stage for 15 patients classified as having carcinoma of stage II Histopathological study revealed potential spread to the cervices in 13 cases eight of them were grouped in the final staging as stage I and the remainder as stage II Table II gives an analysis of the 12 patients in whom carcinoma was no longer detected a secondary curettage or was classified as carcinoma in situ We compared these cases with hysteroscopy hysterosalpingography and primary curettage

The staging performed on the basis of hysterography (49 patient) is presented in Table IV The ma

Table III *The findings from hysteroscopy hysterography and primary curettage in patients with no carcinoma in the secundary curettage*

Secondary curettage		Hysteroscopy hysterography and primary curettage Clin st I	Clin st II	Suspect II	Isthmic	No ca	No curettage	No fract	Clin st III IV
Hysteroscopy									
No carcinoma	11	8	—	—	1	2	—	—	—
Ca in situ	1	1	—	—	—	—	—	—	—
Hysterography									
No carcinoma	11	5	1	2	—	—	3	—	—
Ca in situ	1	1	—	—	—	—	—	—	—
Primary curettage									
No carcinoma	11	8	—	1	—	—	—	2	—
Ca in situ	1	1	—	—	—	—	—	—	—

Table IV *Correlation between hysterography and the final clinical stage*

Hysterography		Final clinical stage St I	St II	St III IV
Clin st I	38	31	6	1
Clin st II	4	1	3	—
Suspect II	7	4	3	—
Total	49	36	12	1

Table V *Correlation between hysteroscopy and the final clinical stage*

Hysteroscopy		Final clinical stage St I	St II	St III IV
Clin st I	36	34	2	—
Clin st II	17	—	15	2
Isthmic	8	5	3	—
Total	61	39	20	2

jority were classified as a change of stage I However the spread to the isthmus was seen in six of 38 cases on the basis of other investigations There was suspicion of cervical spread in seven cases In the final staging four were placed in stage I and three in stage II Hysteroscopy was performed on 61 patients Staging done on the basis of hysteroscopy and its reference to the final staging are presented in Table V Only two of the 36 changes classified as stage I proved to be of stage II on the strength of other investigations All of the stage II tumors were confirmed as regards cervical spread Two cases revealed also spread to the adnexa Eight carcinomas extended to the isthmic region and five of them all Ib lesions were classified as lesions of stage I The spread to the cervical side was shown histologically in three cases Table VI compares the HSG finding with the hysteroscopy finding

DISCUSSION

We have employed the above techniques in parallel during the last few years The studies were conducted successively in the course of the same day before the first course of intrauterine readiotherapy

Fractionated curettage is one of the basic studies in the determination of spread even though the information it yealds contains sources of error for instance contamination from cervix to corpus and vice versa occurs readily In addition definition of the os internum and the isthmic area is difficult Curettage provides important information about the degree of differentation of the tumor and is thus of assistance in drawing up a treatment scheme and prognosis

We regard hysterography as suitable especially for elucidating the anatomy of the cervical canal and the cavity of the corpus when choosing between different modes of treatment (radium post loading device external radiotherapy)

Direct examination of the uterine cavity by hysteroscopy gives in our opinion the most reliable picture when the boundary between stages I and II is being defined It was possible to demonstrate carcinoma like tissue hysteroscopically in 10 of the 12 cases in which carcinoma tissue was no longer detected at secondary curettage With operative optics it is possible to obtain a specimen from even a small area and hysteroscopy performed immediately before curettage makes for more accurate guiding of the curette to the neoplasm site (2) The clinical benefit from accurate determination of the spread is important in the planning of further treatment especially the type of intrauterine radiation and the radicality of surgery

REFERENCES

1 Hilfrich H J Almendral A C Flaskamp D Hofman P Untersuchungen uber die diagnostische Bedeutung der Hysterographie beim Corpuscarzinom Geburtsh u Frauenhailk 29 346 1969
2 Joelsson I Levine R & Moberger G Hysteroscopy as an adjunct in the determining the extent of carcinoma of the endometrium Am J Obstet Gynecol 3 696 1971
3 Joelsson I Sandri A & Kottmeier H L Carcinoma of the uterine corpus A retrospective survey of individualized therapy Acta Radiol Suppl 334 1973

Table VI *Correlatation between the findings from hysterography and hysteroscopy*

Hysterography		Hysteroscopy St I	St II	Isthmic	See below
Clin st I	38	19	4	6	9[1]
Clin st II	4	—	3	—	1[2]
Suspect II	7	5	2	—	—
Total	49	24	9	6	10

[1]No hysteroscopy 6 no carcinoma 3
[2]No carcinoma

4 Joelsson I Methods of diagnosis and staging of corpuscarcinoma Acta Obstet Gynecol Scand Suppl 65 89 1977
5 Johnsson J E Hysterography and diagnostic curettage in carcinoma of the uterine body Acta Radiol Suppl 326 1973
6 Kottmeier H L Carcinoma of the corpus uteri diagnosis and therapy Am J Obstet Gynecol *78* 1127 1959
7 Neuwirth R Hysteroscopy Volume 8 in the series Major problems in Obstetrics and Gynecology
8 Norman O Hysterography in cancer of the corpus of the uterus Acta Radiol Suppl 79 1950
9 Parsons L Cesare F Wertheim hysterectomy in the treatment of endometrial carcinoma Surg Gynecol Obstet *108* 582 1959
10 Obolensky W & Zürcher W O Der Gefässinflux bei Hysterographien als verdächtiges Zeichen auf Korpuskarzinoma Geburtsh u Frauenheilk *24* 8 1964
11 Vuopala S Diagnostic occuracy and clinical applicability of cytologic and histological methods for investigating endometrial carcinoma Acta Obstet Gynecol Scand Suppl 70 1977

Submitted for publication June 6 1978

P Liukko M D
Department of Obstetrics and Gynecology
University Central Hospital
20520 Turku 52
Finland

Acta Obstet Gynecol Scand 58 279–281 1979

INTRAUTERINE PROGESTERONE CONTRACEPTIVE SYSTEM AS AN ALTERNATIVE IN CASES WHERE CONVENTIONAL IUD S ARE UNSUITABLE

P Ylöstalo P Rantakylä P A Järvinen and E Kauppila

From the Department of Obstetrics and Gynecology University of Oulu Finland

Abstract A progesterone intrauterine device (IUD) Progestasert[R] was prescribed for 25 patients unable to use an ordinary non hormonal IUD Both the amount of menstrual bleeding and the discomfort was observed to decrease more often than increase during the period of use of the progesterone IUD Hemoglobin hematocrit and the serum iron levels either remained static or increased Continuation rate was 76 per cent after one year The authors consider Progestasert[R] a suitable alternative to the ordinary non hormonal IUD in women with dysmenorrhea or menorrhagia and tho e in whom a previous *IUD* had been associated with pain or increased menstruation

The intrauterine contraceptive device (IUD) is a widely used alternative to oral contraceptives Increased menstrual blood loss and pain however are acknowledged side effects (7) and the major reasons for discontinuation or contraindication to the use of IUD s Studies published over the last 4 years have shown an increase of 70-120 per cent in menstrual blood loss when compared with the pre insertion cycles with some variation according to the type of IUD (1 3 6)

The purpose of this work was to investigate the effect of an intrauterine progesterone contraceptive system a Progestasert[R] IUD (ALZA Corporation Palo Alto U S A) releasing 65 µg progesterone daily in patients who had suffered from heavy painful menstrual bleeding while using other contraceptive IUD s or had primary dysmenorrhea or menorrhagia being therefore unable to use a conventional IUD

PATIENTS AND METHODS

The investigation covered 25 patients with the indications as shown in Table I for insertion of a Progestasert[R] IUD 13 of the patients had previously been using a Cu T 200 IUD and 12 patients experienced either dysmenorrhea or menorrhagia which had prevented the insertion of any other IUD

Before the insertion of the Progestasert[R] the patients were divided into four groups on the basis of a subjective assessment of the degree of menstrual pain and the amount of menstrual bleeding i e none mild moderate severe During the patient s first visit blood was taken for the estimation of hemoglobin (Hb) hematocrit (Hct) and serum iron (S-Fe) and a Pap smear was taken before insertion of the progesterone IUD The patients were seen post insertion at 3 6 and 12 months when the amount of menstrual blood loss and pain were recorded and the laboratory tests were repeated *The number of defaulters is indicated in the Table* II None of the patients received iron therapy

RESULTS

Table II shows the subjective assessments of menstrual blood loss and pain before the insertion of the Progestasert[R] IUD and at 3 6 and 12 months thereafter

The amount of bleeding subjectively decreased in 13 cases and increased in 2 and in remaining cases it was unchanged

After one year of use 7 patients stated they experienced less pain and 2 suffered from increased pain and in remaining cases no changes were observed

The mean and S D values of hemoglobin were before the insertion of the Progestasert[R] IUD 129±1 1 g/l and after one year of its use 131±1 0 g/l of hem

Table I *Indications for the insertion of a progesterone IUD*

Indication	No of pat
The previous IUD caused	
increase in menstrual blood loss	10
increase in menstrual blood loss and cramps	2
pregnancy during the use of IUD	1
Menorrhagia	7
Menorrhagia and dysmenorrhea	5
Total	25

Table II *Menstrual blood loss and cramps before and after the insertion of the progesterone IUD No of patients in different groups*

	Degree of complaints				
	Severe	Mod	Mild	None	Total
A Menstrual blood loss					
Before insertion	11	13	1	—	25
Cycles after insertion					
at 3 months	4	8	9	—	21
6 months	1	13	3	—	17
12 months	2	7	10	—	19
B Menstrual cramps					
Before insertion	3	4	4	14	25
Cycles after insertion					
at 3 months	—	2	3	16	21
6 months	—	—	5	12	17
12 months	1	2	—	16	19

atocrit 39 9±3 6 per cent and 40 1±3 3 per cent and of serum iron 15 9±6 9 μmol/l and 17 3±5 9 μmol/l respectively No significant changes occurred in these hematological values before and after the insertion of Progestasert^R

During the therapy the Progestasert^R IUD was removed from 4 patients because of acute tubo-ovarian infection at 6 months in one case abnormal bleeding at 1 and 6 months in 2 cases heavy and pain enstruation at 3 months in one case One patient ped out because of changing her place of resi e There were no spontaneous expulsions One ase was further complicated by an extrauterine pregnancy 11 months after insertion Altogether 6 patients had intermenstrual bleeding amounting to spotting After one year all remaining 19 patients wished to continue with Progestasert^R

DISCUSSION

The insertion of an IUD may cause increased menstrual bleeding or pain which is why the conventional non hormonal IUD s are generally considered contraindicated in cases with algomenorrhea and hypermenorrhea (4) A comparative study of the Cu T 200 copper IUD and the Progestasert^R intrauterine progesterone system showed that Cu T 200 increased the amount of menstrual bleeding of 75 per cent of the cases after 3 months of use and in 65 per cent after 6 months of use while Progestasert^R resulted in decreased bleeding in 43 per cent and 40 per cent at the corresponding times (6) According to the subjective estimate of our own patients bleeding decreased during the use of Progestasert^R in about half of the cases and only 8 per cent of the patient reported increased bleeding The unchanged or elevated hemoglobin hematocrit and serum iron values also show that the abundance of menstrual bleeding is generally not a problem during the use of a Progestasert^R IUD not even in the case of hypermenorrheic patients

In our patients series dysmenorrhea more often decreased than increased during the use of Progestasert^R IUD This favorable effect is also shown by the studies of Trobough *et al* (8) in which the prostaglandin $F_{2\alpha}$ content of menstrual blood in patients using the Progestasert^R IUD was diminished when compared with that from women using non hormonal IUD s Prostaglandins have been found to contribute to menstrual pain particularly since inhibitors of prostaglandin synthetase indomethacin and tolfenamic acid have resulted in a good or moderate therapeutic outcome in nearly 90 per cent of the cases of young girls suffering from primary dysmenorrhea (2)

On the basis of our findings we consider the progesterone intrauterine contraceptive system a significant alternative in cases where the conventional non-hormonal IUD is inapplicable as in patients with dysmenorrhea or menorrhagia or subjects who suffer from increased menstrual bleeding and pain during the use of a conventional IUD Our opinion of the suitability of the Progestasert^R IUD is supported by the high continuation rate after one year in our selected series (19/25 = 76 per cent)

Recently a favorable effect of a d norgestrel releasing IUD on menstrual blood loss has been published (5) These results also indicate that by adding a progestagen releasing system to IUD it is possible to extend the scope of its use

ACKNOWLEDGEMENTS

We are grateful to ALZA Corporation U S A and ASTRA Läkemedel AB Sweden for the supply of the progesterone IUD s used in our study

REFERENCES

1 Israel R Shaw S T Jr & Martin M A Comparative quantitation of menstrual blood loss with the Lippes loop Dalkon shield and Copper T intrauterine devices Contraception 10 63 1974
2 Kauppila A & Ylikorkala O Indomethacin and tolfenamic acid in primary dysmenorrhea Europ J Obstet Gynecol Reprod Biol 7 59 1977
3 Liedholm P Rybo G Sjöberg N O & Sölvell L

Copper IUD Influence on menstrual blood loss and iron deficiency Contraception 12 317 1975

4 Martinez Manautou J Experience in Mexico with the intrauterine hormone contraceptive system Ginecol Obstet Mex 40 61 1976

5 Nilsson C G Comparative quantitation of menstrual blood loss with a d norgestrel releasing IUD and a Nova T-copper device Contraception 15 379 1977

6 Rybo G & Bergqvist A Comparison of menstrual blood loss with the Progestasert[R] system and the Cu T 200 Preliminary results To be published

7 Tietze C & Lewit S Evaluation of intrauterine devices Ninth Progress Report of the Cooperative Statistical Program Studies in Family Planning 55 1 1970

8 Trobough G Guderian A Erickson R Tillson S & Pharriss B Dysmenorrhea and the action of intrauterine progesterone on menstrual blood loss and prostaglandin content of menstrual blood In VIII World Congress of Gynec and Obstet Mexico Excerpta Medica ICS 396 193 1976

Submitted for publication October 18 1977

Pekka Ylöstalo M D
Department of Obstetrics and Gynecology
University Hospital
SF 90220 Oulu 22
Finland

A NEW JOURNAI

Journal of Developmental Physiology Volume 1 Number 1 Edited by *Colin T Jones* Blackwell Scientific Publications Osney Mead Oxford OX2 0EL England 1979 Subscription rates Pound sterling 33 00 (U K) 39 50 (overseas) US dollars 90 00 (U S A and Canada) including delivery by air to North America

This new research journal is designed for reports of significant research on any aspect of the scientific study of pregnancy the fetus or the neonate of man or experimental animals Our plans to publish it have been known for sometime and the enthusiastic subscribers and contributors encourages us to believe that it will meet a very real need

Acta Obstet Gynecol Scand 58 283 – 285 1979

MENORRHAGIA DIFFUSE MYOMETRIAL HYPERTROPHY AND THE INTRA UTERINE CONTRACEPTIVE DEVICE A REPORT OF FOURTEEN CASES

Louis H Honore

From the Department of Pathology Vancouver General Hospital Vancouver B C Canada

Abstract Fourteen uteri removed for IUD associated menorrhagia were studied Twelve of these IUD-bearing uteri showed pure diffuse myometrial hypertrophy the other two uteri were enlarged as a result of multiple leiomyomas in one case and extensive deep adenomyosis in the other The incidence of pure myometrial hypertrophy in the IUD group was far in excess of that observed in a control non IUD-bearing menorrhagia series where leiomyomas and/or deep adenomyosis were mostly responsible for the uterine enlargement

The obstetric and gynecologic complications of the intrauterine contraceptive device (IUD) have been extensively documented (5 6 9 13 15 16) Abnormal uterine bleeding especially menorrhagia remains the commonest cause of IUD intolerance and removal within the first few months of insertion and at least three factors have been identified as etiologically significant i e local pressure necrosis with microulcerations (11) vascular congestion platelet thrombi and microhemorrhages in the endometrium not in contact with the IUD (1) increased levels of plasminogen activator in the endometrium and superficial myometrium (12)

Review of the major publications on the IUD reveals no mention of menorrhagia related to diffuse uterine enlargement The problem of uterine enlargement is bedevilled by the lack of agreement as to what constitutes the upper limit of a normal parous uterus Various values have been mentioned ranging from 117 to 125 (2 10 14) and we have adopted 125 grams as enlarged regardless of the clinical associations This purely anatomic diagnosis (10) is justified by the presence of one or more of the following findings symmetric globular enlargment of the corpus enlongation and enlargement of the cervix diffuse or localized (subserosal or submucosal) thickening of the myometrium which often exceeds 2 cms in thickness and hypertrophy of the individual myometrial cell and broadening of the muscle bands as seen microscopically

The present study was confined to menorrhagia associated with benign uterine enlargement (trimmed uterine weight > 125 grams) and its main purpose was to determine whether a similar distribution of pathologic changes underlying the uterine enlargement was present in the IUD group as compared with the non IUD group

MATERIAL AND METHODS

The author personally studied a total of 384 uteri removed for menorrhagia For this present study the control group (women not wearing the IUD at the time of operation) consisted of 254 uteri exceeding 125 grams in weight and satisfying the criteria for benign enlargement these uteri were removed from women aged 26 to 54 years

The IUD group consisted of 19 uteri with 14 exceeding 125 grams in weight and satisfying the critera for benign enlargement These uteri came from women aged 29 to 48 years The IUD s used were the Dalkon Shield and Lippes Loop

In a pilot study it was noted that the incidence of pure myometrial hypertrophy fell above a uterine weight of 150 gram whereas leiomyomas and deep adenomyosis singly or in combination assumed greater importance For this reason the data were analysed using 150 grams as a dividing line

RESULTS

The analysis of the control series is summarized in table I These uteri ranged in weight from 125 to 1 090 grams with the majority lying between 130 to 300 grams and these weights bore no relationship to parity A lower percentage of these uteri (34 65 per cent) weighed less than 150 grams of these 57 95 per cent showed pure myometrial hypertrophy and 42 05 per cent showed myometrial lesions i e leiomyomas and/or deep adenomyosis Among the uteri weighing over 150 grams pure myometrial hypertrophy was

Table I *Control menorrhagia group without IUD*

	Number of cases	Incidence	
		per cent	fraction
Uteri weighing under 150 g	88	34 65	88/254
Uteri under 150 g with pure myometrial hypertrophy	51	57 95	51/88
Uteri under 150 g with leiomyomas and/or deep adenomyosis	37	42 05	37/88
Uteri weighing over 150 g	*166*	*65 35*	*166/254*
Uteri over 150 g with pure myometrial hypertrophy	35	21 08	35/166
Uteri over 150 g with leiomyomas and/or deep adenomyosis	131	78 92	131/166
Total	254	—	—

seen in only 21 08 per cent while uteri with leiomyomas and/or deep adenomyosis predominated (78 92 per cent)

In the much smaller IUD series (table II) only four uteri ranging from 127 to 135 grams weighed under 150 grams (28 42 per cent) and all showed myometrial hypertrophy The remaining ten uteri (71 58 per cent) ranged from 152 to 296 grams (mean weight = 178 9 grams) and eight of these uteri displayed pure myometrial hypertrophy while in one of the remaining two cases uterine enlargement was due to myomas and in the other to diffuse adenomyosis mparison of the incidence of pure myometrial rophy in these two series demonstrated a strik reponderance of this lesion in IUD series in both categories of uteri examined but especially in the uteri weighing over 150 grams Among the uteri weighing under 150 grams the incidence of pure myometrial hypertrophy was 57 95 per cent in the control series and 100 per cent in the IUD series among the uteri weighing over 150 grams the incidence of myometrial hypertrophy was 21 08 per cent in the control series and 80 per cent in the IUD series

DISCUSSION

The incidence of uterine enlargement due to pure myometrial hypertrophy in our IUD series is *significantly* increased as compared with the control series but the question arises as to whether the myometrial hypertrophy is causally related to the menorrhagia Some causes of abnormal uterine bleeding can be excluded such as endometrial hyperplasia polyp or carcinoma postabortal metropathy nonspecific endometritis severe superficial adenomyosis and submucosal leiomyomas Extensive histologic study showed only occasional minute foci of pressure necrosis in areas of contact as described by Moyer *et al* (11) We cannot rule out microaneurysms of the endometrium not in contact with the IUD (1) as no ultrastructural studies were done nor can we exclude an excess of plasminogen activator in the endometrium and superficial myometrium (12) as no assay of this substance was undertaken The only significant factor therefore remains the diffuse myometrial hypertrophy which we consider responsible for the menorrhagia as suggested by many authors in the past (4 7 17) It is conceivable though unproven that an abnormally thick myometrium is unable to promote adequate hemostasis during menstruation The mechanism of myometrial hypertrophy in these IUD-bearing uteri is obscure but is clearly not related to outflow obstruction associated pregnancy or obvious hyperestrinism since these women showed no tendency to endometrial hyperplasia Nor can the myometrial hypertrophy be attributed to chronic overstretch of the uterus by oversized devices which had been tolerated for up to three years without significant discomfort and grossly there was no undue expansion of the uterine cavity or burrowing of the IUD into the *myometrium*

The most likely mechanism is related to locally released prostaglandins by the IUD as shown experimentally in the rat uterine horn (3) The rarity of significant myometrial hypertrophy with the IUD may reflect the extreme variability of response of the endometrium to the IUD *in terms* of local prostaglandin release (8) these women may release unusually large amounts of PGF_{α} which is a potent stimula

Table II *Menorrhagia associated with IUD*

	Number of cases	Incidence	
		per cent	fraction
Uteri weighing under 150 g	4	28 42	4 14
Uteri under 150 g with pure myometrial hypertrophy	4	100	4/4
Uteri weighing over 150 g	10	71 58	10/14
Uteri over 150 g with pure myometrial hypertrophy	8	80	8 10
Uteri over 150 g with adenomyosis/leiomyomas	2	20	2/10
Total	14	—	—

of the myometrium This chronic excess of $PGF_{2\alpha}$ though inadequate to cause significant spasm and clinical discomfort may lead to progressive myometrial hypertrophy over a variable period of time

Finally most of these uteri also showed cervical elongation (length >3 5 cm) and concentric enlargement (diameter of cervical cylinder >3 cm) No explanation of this phenomenon is available but it is possible that the string of the IUD in the canal may also locally release prostaglandins which may have an effect on the submucosal fibrovascular tissues and the myocervix It might be rewarding to pay more attention to the cervix in studying the contraceptive action of the IUD

REFERENCES

1 Ancla M DeBrux J & Simon P Aneurysmal microthrombosis associated with intrauterine devices in the human endometrium An electron microscopic study Lab Invest *17* 61 1967
2 Armed Forces Institute of Pathology The Autopsy Washington D C p 41 1951
3 Chaudhuri G Influence of Indomethacin an inhibitor of prostaglandin synthesis on IUD mediated increased mobility and hypertrophy of the rat uterine horn *In* Analysis of Intrauterine Contraception (ed Hefnawi F and Segal S J) p 447-480 North Holland Publishing Co Amsterdam Oxford American Elsevier Publishing Company Inc New York 1975
4 Curtis A H Hypertrophy of the uterus Am J Obstet Gynecol *50* 748 1945
5 Hallatt J G Ectopic pregnancy associated with the intrauterine device Am J Obstet Gynecol *125* 754 1976
6 Hefnawi F & Segal S J Analysis of intrauterine contraception North Holland Publishing Company Amsterdam Oxford American Elsevier Publishing Company New York pp 333-476 1975
7 Hillier H Micromyomas of the uterus with severe menorrhagia a syndrome Am J Obstet Gynecol *87* 163 1963
8 Hillier K & Kasonde J M Prostaglandin E and F concentrations in human endometrium after insertion of intrauterine contraceptive device Lancet *1* 15 1976
9 Kahn H S & Tyler C W Mortality associated with the use of intrauterine devices JAMA *234* 57 1976
10 Lewis P L Lee A B H & Easler R E Myometrial hypertrophy A clinical pathologic study and review of the literature Am J Obstet Gynecol *84* 1032 1962
11 Moyer D L Mishell D R Jr & Bell J Reactions of the human endometrium to the intrauterine device I correlation of the endometrial histology and the bacterial environment of the uterus following short term insertion of the IUD Am J Obstet Gynecol *106* 7 1970
12 Poon C H Shaw S T Jr & Moyer D L Protease activity in uterine fluid and tissue associated with intrauterine devices Paper presented at the 21st Annual Meeting of the Pacific Coast Fertility Society October 1973 Palm Springs California
13 Roland M The Response to Contraception W B Saunders Company Philadelphia London Toronto p 111 132 1973
14 Saphir O Autopsy Diagnosis and Technique 2nd Edition Paul B Hoeber Inc New York p 374 1946
15 Weekes L R Complications of intrauterine contraceptive devices J Ntl Med Assoc *67* 1 1975
16 Wheeler R G Duncan G W & Speidel J J Intrauterine Devices Development Evaluation and Program Academic Press New York San Francisco London passim 1974
17 Williams J T & Kinney T D Myometrial hypertrophy (so-called fibrosis uteri) Am J Obstet Gynecol *47* 380 1947

Submitted for publication October 28 1977

Louis Honore
Department of Laboratories
Grace General Hospital
St John s Newfoundland
Canada

ANNOUNCEMENT

International Symposium on Adrenal Androgens is to be held at the University of Siena Italy October 7 9 1979

Scientific Committee A R Genazzani Sienta Italy G Giusti Florence Italy P C MacDonald Dallas U S A W D Odell Torrance U S A P K Siiteri San Francisco U S A J H H Thijssen Utrecht Holland A Vermeulen Ghent Belgium

Sponsors The American Express Company under the auspices of the Italian Society of Obstetrics and Gynaecology the Italian Society of Endocrinology the Italian Society of Fertility and Sterility and the C N R project Biology of Reproduction

Topics

Androgen secretion by human adrenal and testis cells in culture

- Hormonal factors controlling and stimulating adrenal androgen secretion
- Adrenal androgen metabolism and conversion in humans
- Adrenal androgens in pregnancy in prepuberty puberty adult life ageing and in postmenopausal women hirsute and obsese subject
- Enzymatic adrenal factors

Adrenal androgens and endometrial cancer

- Adrenal androgen effects on bone metabolism and on the hypothalamus pituitary gonadal axis

Round Table Adrenal androgens the future

Invited Speakers G Abraham Rolling Hills U S A D Anderson Manchester England A Genazzani Siena Italy G Giusti Florence Italy P MacDonald Dallas U S A A Neville Sutton England B Nordin Leeds England W Odell Torrance U S A C Pintor Cagliari v J Poortman Utrecht Holland M Serio Florence P Siiteri San Fransisco U S A P Sizonenko Gen Switzerland J Thijssen Utrecht Holland D Tulsky Boston U S A A Vermeulen Ghent Belgium

fficial language English

Researchers are invited to submit 250 word abstracts of unpublished work for oral or poster presentation before June 15 1979 A limited number of free communications will be selected for presentation and published with the invited lectures in the proceedings Abstracts of invited lectures free communications and posters will be published in a separate volume

Scientific Secretary

Professor A R Genazzani
Centro di Fisiopatologia della Riproduzione
Università di Siena
Via Paolo Mascagni 46
53100 SIENA Italy
Tel 0577/49 06 44051

IXth World Congress of Gynecology and Obstetrics is to be held October 25 31 1979 in Tokyo Japan

Official languages English French Spanish and Ja anese

Scientific Program

Special lectures

Reproductive endocrinology by Prof Kenneth J Ryan Harvard Medical School U S A

Comparative aspects of fetal differentiation by Prof Alfred Jost College de France France

Recent progress in gynecologic oncology by Prof Per Kolstad Norwegian Radium Hospital Norway

- Plenary sessions

Social aspects of obstetrics and gynecology includ g contraception

The climacteric and postmenopause including hormone therapy

Endocrinology of the menstrual cycle

Physiopathology of intrauterine fetal growth

Reproductive immunology

The role of obstetric management in reducing fetal mortality and morbidity

Premalignant lesions of the female genital tract

In addition there are *Correlated Seminars* Seminars a d *Free Communications* covering wide range of topics of current interest

Social Program and *Program for Accompanying Persons*

Deadlines

Early registration July 31 1979

Application Free communication papers films and scientific exhibits February 28 1979

Those who are interested in attending the Congress are invited to write to

Secretariat
IX World Congress of Gynecology and Obstetrics
c/o Simul International Inc
Kowa Bldg No 9
1 8 10 Akasaka Minato-ku
Tokyo 107 Japan

Acta Obstet Gynecol Scand 58 287–293 1979

BIOLOGICAL FATE OF METHENAMINE IN MAN

Absorption renal excretion and passage to umbilical cord blood amniotic fluid and breast milk

Lars Göran Allgen Göran Holmberg Birgitta Persson and Bo Sörbo

From the Clinical Chemistry Central Laboratory and the Department ofGynecology and Obstetrics S t Eriks Hospital Stockholm and the Department of Clinical Chemistry University of Linköping Linköping Sweden

Abstract Methenamine hippurate was administered orally as tablets or granules to healthy volunteers Plasma concentrations of methenamine reached a maximum 1 2 hours after a single dose and then declined with a half life of about 4 hours The apparent distribution volume was similar to that of total body water Renal clearance of methenamine was somewhat lower than that of creatinine In cross-over experiments over six days methenamine recovered in the urine corresponded to about 80 per cent of the dose given per 12 hours slightly lower values being obtained from granules than from tablets The efficient renal elimination of methenamine was confirmed in similar studies on patients post-operatively

Methenamine hippurate was also given to healthy pregnant women during labor a few hours before expected delivery Methenamine was found to pass the placental barrier The concentration of methenamine in umbilical cord plasma was low but reached the level in maternal plasma after about 4 hours In amniotic fluid the methenamine concentration was low and varying No correlation was obtained to the maternal or umbilical cord plasma levels

The methenamine concentration in breast milk was of the same magnitude as in maternal plasma It is concluded that methenamine may be safely given to pregnant and lactating women with respect to the wellbeing of the child

Methenamine (hexamethylenetetramine) was introduced in 1895 by Nicolaier (9) as a urinary tract antiseptic It has since then found wide spread use in the form of various salts given orally for treatment of urinary treact infections (13) and for prophylactic purposes in connection with gynecologic or urologic surgery The bactericidal action of the drug has been attributed to slow hydrolysis of methenamine in acid urine with liberation of formaldehyde while development of bacterial resistance seems impossible A number of studies (3 5 7 13) have been concerned with the relation between urinary formaldehyde and antibacterial activity after administration of methenamine to human subjects whereas less attention has been paid to the distribution and elimination of the intact drug Scudi and Reinhard (11) administered methenamine mandelate to dogs and found its distribution volume to approximate the total volume of body water Furthermore they found the renal clearance of intravenously administered methenamine to be somewhat lower than that of creatinine and concluded that a tubular reabsorption of methenamine took place Knight *et al* (5) determined serum levels of methenamine mandelate in human beings but the results showed large variations and neither could values for the serum half life nor for renal clearance be obtained About 50 per cent of the administered dose was recovered in urine during 24 hours following administration This study was probably hampered by an imprecise analytical technique

We have now studied the distribution and elimination of methenamine in human beings after oral administration of methenamine hippurate (Hiprex[R] in USA Urex[R] Riker Laboratories) using an analytical method developed for this purpose The drug is usually given as tablets which however may cause gastrointestinal irritation A granular preparation has recently been developed as an alternative formulation with less side effects and therefore we also compared the absorption of methenamine from tablets and granules

It is generally accepted that adequate treatment of asymptomatic bacteriuria during pregnancy significantly lowers the frequency of pyelitis and premature deliveries Methenamine has been recommended for such prophylactic treatment The question then arises if methenamine can pass the placental barrier at concentrations which might be harmful to the fetus We

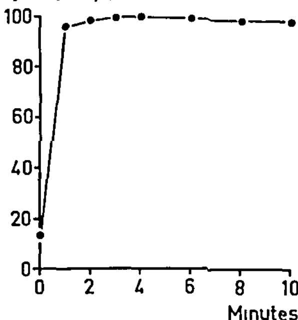


Fig 1 Hydrolysis of methenamine Samples containing 0 06 μmoles methenamine in 2 0 ml 7 1 per cent TCA were heated in a boiling water bath for the times indicated For maldehyde was then determined according to Nash (8) as described in Methods

therefore determined methenamine concentrations in umbilical cord blood and in amniotic fluid obtained delivery of pregnant women treated with a stan dose of the drug Furthermore prophylactic of lactating mothers with methenamine has advocated on the basis of an increased maternal susceptibility to infections in the puerperium The possibility that the child will recieve significant (and possibly harmful) quantities of methenamine with the milk must obviuosly be considered This prompted us to measure methenamine concentrations in milk from lactating women treated with methenamine

MATERIAL AND METHODS

Drug administration and collection of plasma and urine Eight healthy volunteers belonging to the laboratory staff 2 males and 6 females age 23 50 years participated in the study In addition a clinical material of 6 patients who had undergone vaginal surgery with postoperative indwelling catheter and Uribag[R] permitting closed urine sampling was studied Their age range was 30-79 years Methenamine hippurate was given as 1 g tablets or as 1 g granules dissolved in about 100 ml water either as a single dose or twice daily *i e* each twelfth hour The latter regimen was used when tablets and granules were compared with respect to the urine elimination of methenamine A crossover schedule was used where tablets were given for three days and granules for three days or in the reverse order

Blood samples were collected in heparin tubes (Vacutainer[R]) plasma was separated by centrifugation and frozen if not analyzed on the same day For determination of plasma concentration curves samples were taken before and at 15 30 60 120 240 and 360 minutes after dose Urine was collected in plastic bottles containing 5 g sodium bicarbonate powder to prevent methenamine hydrolysis during collection and before analysis 12 hour portions were collected corresponding to the dose periods Urine was stored at +4 C if analyzed within 24 hours or frozen at 20 C if analyzed later on When renal clearance studies were performed after a single dose of methenamine urine was collected in the time intervals 2-4 and 4-6 hours after the dose *i e* during the exponential decrease of plasma methenamine concentrations (see Results)

Collection of umbilical cord plasma amniotic fluid and breast milk Methenamine hippurate was given to 8 healthy pregnant women in labor who volunteered for this study 1 g tablets were given as a single dose a few hours before expected delivery Amniotic fluid was collected by amniocentesis or on rupture of membranes At delivery cord blood was collected and about 1 hour later a venous blood sample was taken from the mother A number of analyses including urea and creatinine were made on the collected amniotic fluid (2) to exclude contamination with maternal urine The passage of methenamine into milk was studied in 4 lactating mothers in the maternity ward They were given 1 g methenamine hippurate as a single dose and four to five hours later the child was breast fed and thereafter the remaining milk was mechanically pumped out for analysis In 2 additional cases samples of milk were collected just before and after feeding and venous blood samples were collected from the mothers The weight of the children before and after feeding was recorded and the difference taken to represent the amount of milk fed The samples were analyzed within the same day

Analytical methods Methenamine determination was based on hydrolysis of the compound to formaldehyde in acid solution and subsequent colorimetric determination of formaldehyde either by use of the chromotropic acid reaction (6) or the reaction with acetylacetone and ammonia according to Nash (8) The two methods for determination of formaldehyde were found to give identical results if proper corrections for biological blanks were carried out The method of Nash was preferred as it gave lower biological blanks for plasma and was more convenient to use Aqueous solutions of analytically pure hexamethylenetetramine and of titrimetrically assayed formaldehyde were used as standards Pilot experiments showed that protein-containing samples (plasma amniotic fluid and breast milk) could be deproteinized with quantitative recovery of methenamine by precipitation with trichloroacetic acid (TCA) Methenamine in the TCA-containing supernatant was then quantitatively hydrolyzed to formaldehyde by heating for 5 minutes in a boiling water bath (Fig 1) This time of hydrolysis is considerably shorter than that used by Knight *et al* (5) in their method for determination of methenamine which may explain the improved results obtained with the present method It should be noted that our method for determination of methenamine will include any free formaldehyde

Table I *Pharmacokinetic data derived from single oral dose studies of 1 g methenamine hippurate (3 13 mmol) in four normal female volunteers*

Subject No	Age (years)	Body weight kg	Formulation used	$T_{½}$ (hours)	AUC (μmol/l hours)	Vd_{area} (l/kg)	Vp (ml/min)
14	27	45	Tablets	3 75	582	0 647	89 6
15	23	51	Tablets	4 45	524	0 751	99 5
17	27	50	Granules	3 50	624	0 510	84 3
18	25	54	Granules	3 75	527	0 594	99 0
Mean				3 86	563	0 601	93 1

present in the sample This was of no consequence in the present investigation as free formaldehyde has not been detected in the blood (12) after administration of methenamine and the levels of free formaldehyde in urine (3 7) represent only 4-6 per cent of the latent formaldehyde present as methenamine

Methenamine was determined in plasma amniotic fluid and milk as follows To 1 0 ml sample or standard solution 2 5 ml 10 per cent (w/v) TCA was added After mixing the precipitate was removed by centrifugation 2 0 ml of the clear supernatant was transferred to a glass stoppered test tube and heated for 5 minutes in a boiling water bath The tubes were then cooled in tap water and 2 0 ml reagent according to Nash (8) (150 g ammonium acetate 3 ml glacial acetic acid 2 ml acetylacetone and distilled water to 1 l) was added The tubes were then heated at 58 C for 5 minutes cooled to room temperature and the absorbances of the samples were read at 412 nm against a reagent blank For milk an individual sample blank was also included in which the Nash reagent was replaced by water

The methenamine concentration was read from the simultaneously determined standard curve The latter was linear up to at least 140 μmol/l corresponding to an absorbance reading of 1 00 When methenamine was added to plasma at final concentrations of 50-150 μmol/l recoveries of 91 101 per cent were obtained It was also verified that no loss of methenamine occurred to the fat phase during the analysis of milk

Urine was analyzed for methenamine after mixing 20 μl of sample with 2 0 ml 10 per cent (w/v) TCA Hydrolysis and further analysis was then performed as described above The validity of the urine collection procedure was verified by reanalyzing urine samples after three days of storage No significant changes of methenamine concentrations were observed

Creatinine was determined in plasma and urine by the use of an alkaline picrate method on the Technicon Autoanalyzer system involving dialysis of the samples

Calculations Linear and semilogarithmic plots of plasma methenamine concentration versus time were made for each single dose experiment The terminal linear slope of the semilogarithmic plot gave the half life of elimination ($T_{½}$) and from the linear plot the area under the plasma concentration curve (AUC) was calculated by the trapezoidal rule (14) and by integration for the remaining portion beyond the last sampling point The apparent volume of distribution (Vd_{area}) and plasma clearance (Vp) were then calculated from the dose given T/ and AUC according to Wagner (14) assuming complete bioavailibility of the compound Renal clearance of methenamine was calculated from the amount of compound excreted in the 2-4 and 4-6 hour periods after dose divided by the plasma concentration corresponding to the mid point of each period The latter was obtained from the semilogarithmic plot of the plasma concentration curve Endogenous creatinine clearance was calculated from the amount of creatinine excreted in the same time periods divided by the average of plasma creatinine concentrations at the beginning and end of each sampling period

RESULTS

After the administration of a single dose of 1 g methenamine hippurate as tablets or granules plasma levels of methenamine rose fairly rapidly as shown in Fig 2 The results suggested a more rapid absorption of the granules but no definite conclusions on that point could be drawn due to the small number of subjects studied Maximum plasma levels of 70-100 μmol/l were obtained within 1 2 hours and thereafter the plasma concentration declined monoexponentionally The half lives of elimination apparent distribution volumes and plasma clearances of methenamine were then calculated and the results are given in Table I A mean half life of 3 9 hours was obtained demonstrating a slow elimination from the body The apparent distribution volume found (0 60 l/kg) is very similar to reported values for total body water in human beings (14) The plasma clearance values (Table I) were found to be of the same magnitude as simultaneously determined renal clearance values (Table II) indicating that methenamine is mainly eliminated by renal excretion However the renal clearance values (mean 71 ml/min) were somewhat lower than the plasma clearance values (mean 93 ml/min) which may be due to the existence of extra renal routes of elimination or more probably to underestimations of renal clearance resulting from in

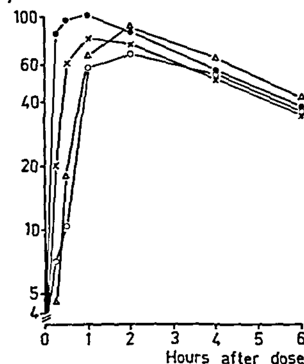


Fig 2 Plasma concentrations of methenamine in four volunteers after 1 g methenamine hippurate The drug was given either as tablets or granules (see Table I)
Δ—Δ Subject 14 O—O Subject 15 ●—● Subject 17 ×—× Subject 18

lete emptying of the bladder during the short lection periods employed The renal clearance of methenamine was furthermore found to be somewhat lower than that of creatinine (Table II)

The renal excretion of methenamine from tablets and granules of methenamine hippurate was then studied after multiple doses of the drug according to the therapeutic regimen now recommended (6) *i e* 1 g methenamine hippurate each 12th hour Tablets or granules were given to volunteers for 3 days in a cross over study The results (Fig 3) demonstrated that about 80 per cent of the methenamine administered was excreted in the urine within 12 hours The recovery of methenamine in urine was slightly higher from tablets than from granules the two mean values being 83±1 9 per cent (mean±SEM) and 78±1 8 per cent respectively

When the renal excretion of methenamine was studied in patients 24 hour collection periods were used for practical reasons The results are given in Fig 4 The recovery of methenamine in urine was of the same order of magnitude as that obtained from volunteers being 76±2 7 per cent in the case of tablets and 73±3 5 per cent in the case of granules Thus somewhat lower values were obtained in patients possibly due to difficulties in quantitative urine collection from patients in the wards

The passage of methenamine across the placental barrier was studied by determination of methenamine in umbilical cord plasma collected at delivery The results are given in Fig 5 As samples had to be collected at delivery the time interval between dosing and sampling varied from case to case The methenamine concentration in umbilical cord plasma compared to that in maternal plasma was initially low but after about four hours the umbilical cord plasma level had increased to about the same level as that in maternal plasma The results thus demonstrate a slow passage of methenamine over the placental barrier without any evidence of accumulation of the drug in the fetal circulation

Methenamine was also determined in amniotic fluid collected either before or at delivery as described above The concentration of methenamine in amniotic fluid varied markedly between 4 and 63 μmol l (Fig 6) There was no correlation between the am-

Table II *Renal clearance of methenamine (MA) and creatinine (Cr) in four normal female volunteers*

Subject No	MA-clearance (ml/min) 2–4 h[1]	4–6 h[1]	2–6 h[1]	MA-clearance/ body surface (ml/min/m)	Cr-clearance/ body surface (ml/min/m²)	Clearance ratio MA/Cr
14	58	40	49	35	43	0 81
15	102	102	102	66	60	1 10
17	55	73	64	42	47	0 89
18	77	58	68	42	64	0 66
Mean			71	46	54	0 87

1) time interval a er 1 g oral dose

Fig 3 Urinary excretion of methenamine after oral administration of 1 g methenamine hippurate each 12th hour to healthy volunteers
Left panel Tablets given days 1 3 granules days 4-6 Mean values and ranges (indicated as vertical bars) from 3 subjects
Right panel Granules given days 1 3 tablets days 4-6 Mean values and ranges from 3 subjects

Fig 4 Urinary excretion of methenamine after oral administration of 1 g methenamine hippurate each 12th hour to patients
Left panel Tablets given days 1 3 granules days 4-6 Mean values and ranges (indicated as vertical bars) from 3 patients
Right panel Granules given days 1 3 tablets days 4-6 Mean values and ranges from 3 patients

motic fluid concentration and time after dose nor any correlation to the concentration in umbilical cord or maternal plasma

When breast milk was analyzed five hours after a 1 g oral dose of methenamine hippurate to 4 lactating women a mean concentration of 50 μmol methenamine/l (range 48 52 μmol/l) was found Similar determinations were also performed together with assays of methenamine in maternal plasma on 2 additional cases (Table III) The concentration in milk was found to be of the same magnitude as in maternal plasma and thus no accumulation of methenamine occurs in milk It may also be observed (Table III) that some decrease of the methenamine concentration in milk apparently took place during feeding

DISCUSSION

The present study demonstrates that methenamine is readily absorbed when given as hippurate in the form of tablets or granules Plasma peak levels of 70-100 μmol/l were thus observed at 1 2 hours after a single dose of 1 g of the drug These results may be related to those of Knight *et al* (5) who reported that serum peak levels of methenamine corresponding to 65 μmol/l were obtained at 6 hours following a single dose of 3 g methenamine mandelate This dose was 3 fold higher than that used in the present study (the molecular weights of the hippurate and mandelate of methenamine are very close) but nevertheless resulted in lower serum peak levels occurring at a later time These discrepancies may be attributed to differences in the experimental technique used the most important probably being that Knight *et al* administered the drug as enteric-coated pills The apparent distribution volume of methenamine obtained in the present investigation corresponds to that of total body water which is in agreement with the findings of Scudi and Reinhard (11) in dogs There are thus no signs of tissue accumulation of the drug Furthermore these authors reported that renal clearance of methenamine was lower than that of creatinine

Table III *Methenamine (MA) concentration in milk in relation to the concentration in maternal plasma after oral administration of 1 g MA hippurate*

Subject	MA concentration in milk μmol/l				Ratio milk ²⁾/maternal plasma	
	1 feeding (2–3 h)¹⁾		2 feeding (6–7 h)¹⁾		1 feeding	2 feeding
No	before	after	before	after		
16	64 5	53 6	5 0	<5 0	1 04	0 89
19	71 4	70 2	43 7	28 9	1 08	0 88

1) t me after dose to mother
2) mean levels for milk and t (e tra)polated midtime plasm levels for mothers were sed

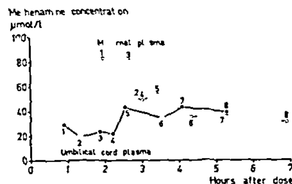


Fig 5 Methenamine concentrations in umbilical cord plasma and maternal plasma after administration of methenamine hippurate (1 g) to women in labor Each mother and child are identified with a number which is in dicated on each plot

which was also observed in the present study Scudi and Reinhard interpreted their findings as indicating a tubular reabsorption of methenamine but their results as well as ours showed some variation and must be considered more suggestive than conclusive in this respect

It was found in the present investigation that the methenamine recovered in the urine in 12 hours after single or multiple doses given to healthy volunteers corresponded to about 80 per cent of the dose There as a small but statistically significant difference be the mean recoveries obtained from tablets (83 cent) and granules (78 per cent) but this is ob- ly of no importance with respect to the therapeutic effect of the drug Similar results 76 and 73 per cent respectively were obtained in patients It may be noted in this context that Knight *et al* (5) reported that when methenamine mandelate was giv en as enteric-coated pills to patients only about 50 per cent of the dose was recovered as methenamine in urine in 24 hours The lower yields obtained by these authors in comparison with those obtained in the present study may be attributed to the different formulation of the drug used and to the fact that the precaution of keeping the urine at an alkaline pH during collection was apparently not observed

In the pregnant women at term it is shown in the present investigation that methenamine passes the placental barrier although at a slow rate (Fig 5) The concentrations reached in umbilical cord blood are on an average lower than in the maternal blood after a single dose Thus there are no signs of accumulation in the fetal circulation As was previously shown there are no signs of tissue accumulation in adults and no reason to suspect such in the fetus

The concentration of methenamine in amniotic fluid was found to vary markedly (between 4 and 63 μmol/l) This is not unexpected as methenamine reaching the fetus will be intermittently excreted with the fetal urine into the amniotic fluid As the amniotic fluid is rapidly renewed by exchange with the maternal circulation (10) the methenamine concentration in amniotic fluid will vary according to the frequency of fetal micturition The methenamine concentrations which we observed in amniotic fluid are however smaller than the peak plasma concentrations observed in adults and there are no reasons to expect this low concentration to be harmful to the fetus It may be noted in this context that the slightly alkaline reaction (pH 7 8) of amniotic fluid prevents the hydrolysis of methenamine to formaldehyde which can be expected to be more harmful to the fetus than the parent compound Our conclusion that methenamine can be safely used in pregnancy is also supported by clinical data reported by Andelman (1) It should furthermore be pointed out that indications for methenamine treatment during pregnancy occur mainly in the second and third trimester The hazard of teratogenicity if any must therefore be very small

When methenamine is given to lactating women the concentration of the drug observed in milk is about the same as that in maternal plasma The amount of

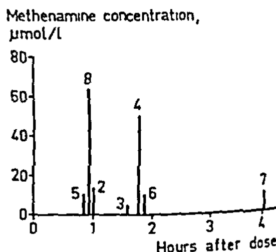


Fig 6 Methenamine concentrations in amniotic fluid after administration of methenamine hippurate (1 g) to the mother Numbers above plots are those given in Fig 5 for identification of mother and child

methenamine received by the child is then of the order of 0 15 0 40 mg with each meal (calculated on the basis of 50 g milk per meal) corresponding to a methenamine dose of 0 05 0 10 mg per kg body weight This value is far below the therapeutic dose given to adults (about 5 10 mg per kg bodyweight) and any untoward effects to the child from this dose is highly unlikely

REFERENCES

1 Andelman M B Bacteriuria of pregnancy treated with a new methenamine salt (methenamine hippurate) J Reprod Med *2* 95 1969

2 Free A H & Free H M *In* Amniotic Fluid Physiology Biochemistry and Clinical Biochemistry *(eds S Natelson A Scommegna M B Epstein) p* 37 Wiley New York 1974

3 Gandelman A L Methenamine mandelate Antimicrobial activity in urine and correlation with formaldehyde levels Brit J Urol *97* 533 1967

4 Jackson J & Stamey T A The Riker method for determining formaldehyde in the presence of methenamine Invest Urol *9* 124 1971

5 Knight V Draper J W Brady E A & Attmore C A Methenamine mandelate Antimicrobial activity absorption and excretion Antibiot Chemother *2* 615 1952

6 Mac Fayden D A Watkins H D & Andersson P R Estimation of formaldehyde in biological mixtures J Biol Chem *158* 107 1945

7 Miller H & Phillips E Antibacterial correlation of urine drug levels of hexamethylenetetramine and formaldehyde Invest Urol *8* 21 1970

8 Nash T The colorimetric estimation of formaldehyde by means of the Haentzsch reaction Biochem J *55* 416 1953

9 Nicolaier A Ueber die therapeutische Verwendung des Urotropin (Hexamethylentetramin) Deutsch Med Wochenschr *34* 541 1895

10 Saunders P & Rhodes P *In* Amniotic fluid Research and clinical application (eds D V I Fairweather & T K A B Eskes) p 8 Excerpta Medica Amsterdam 1973

11 Scudi J V & Reinhard J F Absorption distribution and renal excretion of mandelamine (methenamine mandelate) J Lab Clin Med *33* 1304 1948

12 Seneca H Zinsser H H & Peer P Chemotherapy of chronic urinary tract infections with methenamine hippurate J Urol *97* 1094 1967

13 Seneca H & Peer P Clinical Pharmacology and antibacterial action of methenamine and its salts Med Times *97* 243 1969

14 Wagner J G Biopharmaceutics and relevant pharmacokinetics Drug intelligence publications Hamilton Illinois 1971

Submitted for publication December 12 1977

Lars Göran Allgen M D
Clinical Chemistry Central Laboratory
S t Eriks Hospital
S-112 82 Stockholm
Sweden

ANNOUNCEMENT

European Congress of Obstetric Anaesthesia and Analgesia will take place at the Birmingham Metropole Hotel adjacent to the National Exhibition Centre from the 17th to the 20th September 1979

Further details may be obtained from
Dr J Selwyn Crawford Consultant Anaesthetist
Birmingham Maternity Hospital
Edgbaston
Birmingham B15 2TG
England

International Symposium on Clinical Importance of Surfactant Defects will be held in Hamburg October 31 November 2 1979

Information
Professor Dr P v Wichert
I Medizinische Universitätsklinik
Hamburg Eppendorf
Martinistrasse 5?
D 2000 Hamburg 20
Germany

IX Meeting of the International Study Group for Steroid Hormones will be held in Rome December 1979

Topics
Endocrinological cancer
breast cancer
prostate cancer
Ovarian function and disease

Further information may be obtained from
Professor Carlo Conti
International Study Group for Steroid Hormones
Clinica Medica V Policlinico Umberto I Università di Roma
Roma
Italy

Acta Obstet Gynecol Scand 58 295–299 1979

MINIMAL BRAIN DYSFUNCTION IN CHILDREN BORN IN BREECH PRESENTATION

Stefan Fianu and Ingemar Joelsson

From the Department of Obstetrics and Gynecology at Sabbatsberg Hospital Karolinska Institutet Stockhom and the Department of Obstetrics and Gynecology University of Umeå School of Medicine Umeå Sweden

Abstract The influence of delivery in breech presentation on the occurrence of minimal brain dysfunction (MBD) has been studied Parents of 8 15 year old children were asked to account for behavioral and educational deficits and needs of their children from birth until the date of investigation It was found that among prematurely delivered children the frequency of MBD defined as hyperkinesia and learning disability amounted to about 20 per cent and was similarly distributed between children delivered in breech and in vertex presentation Among term delivered children however the average frequency of hyperkinesia and learning disability amounted to 8 per cent in children born in breech presentation it was 14 per cent while in those born in vertex presentation the corresponding figure was 2 per cent MBD was more common in boys (16 per cent) than in girls (12 per cent)

The concept of specific learning and behavioral disorders in children of normal intelligence is relatively recent The notion was originally introduced by educators and psychologists but along with the development of diagnostic methods in pediatrics a neurogenic basis for underachievements has been uncovered The knowledge that deficits in speech language perception and memory can be the result of a disease localized to certain sites in the cerebral hemispheres has led to the term Minimal brain dysfunction MBD is a composit description of a symptomatology in which the main components are hyperkinesia learning disability speech and language disorders It was found however that in a majority of patients with MBD the brain damage is both minimal and diffuse which renders a localization of the cerebral pathology diffucult to document

MBD is a complex of symptoms diverse in clinical manifestations and presumptive etiological background Enzyme defects biochemical deficiencies of a genetic nature periods of brain anoxia and trauma have been proposed (2 12 14 15) MBD has also been viewed as sequelae of complicated deliveries (2 12) An earlier paper described the relation between birth in breech presentation and the frequency of occurrence of MBD (4) It was reported that children with reading and writing difficulties represented 45 per cent of those born in breech as compared with 26 per cent of children born in vertex presentation The aim of the present investigation has been to further elucidate the relationship between birth in breech presentation and the occurrence of MBD with special regard to problems connected with maturity

MATERIAL AND METHODS

Case reports of children delivered in breech presentation at the Departments of Obstetrics and Gynecology at Sabbatsberg Hospital Allmänna Barnbördshuset and Södersjukhuset during the years 1961 to 1968 (incl) were collected The material was divided in two groups prematurely born children (<2 500 g) and term delivered mature children (>2 500 g) Reference groups were formed for each of these the case reports of the live born infants in vertex

Table I *Characterization of the premature deliveries by maternal age duration of labor parity and sex*

Group	Breech delivery No	Breech delivery %	Vertex delivery No	Vertex delivery %
Maternal age				
<31 years	97	71 3	98	71 0
≥31 years	39	28 7	40	29 0
Duration of labor				
≤20 hours	124	91 2	125	90 6
>20 hours	12	8 8	13	9 4
Parity				
Primiparae	64	47 1	63	45 7
Multiparae	72	52 9	75	54 3
Sex				
Male	56	41 2	71	51 4
Female	80	58 8	67	48 6

Table II *Characterization of the term deliveries by maternal age duration of labor and parity*

Group	Breech delivery No	Breech delivery %	Vertex delivery No	Vertex delivery %
Maternal age				
<31 years	736	76 4	749	78 2
≥31 years	227	23 6	209	21 8
Duration of labor				
<20 hours	796	82 7	805	84 0
≥20 hours	167	17 3	153	16 0
Parity				
Primiparae	281	29 2	257	26 8
Multiparae	682	70 8	701	73 2

Table III *Characterization of the term deliveries by infant sex birth weight and mode of delivery*

Group	Breech delivery No	Breech delivery %	Vertex delivery No	Vertex delivery %
Infant sex				
Male	381	39 6	496	[illegible]
Female	582	60 4	46[illegible]	[illegible]
Birth weight				
2501–4000 g	899	93 4	891	93 0
≥4001 g	64	6 6	67	7 0
Mode of delivery				
Spontaneous	865	89 8	940	98 1
Cesarean sect	98	10 2	18	1 9

presentation filed next in order to each of the infants in breech presentation made up the control groups

As by definition MBD encompasses children with near or above average intelligence all children who attended classes for backward children were excluded from the study

Based on previous experience (4) a questionnaire was designed to be answered by the parents Questions were asked about various aspects of behavior and achievement of the child from birth until the date of investigation Data on maternal factors complications during pregnancy and delivery the infant s birth weight and sex were extracted from the case reports

The studied material is presented in Tables 1–3

RESULTS

The 274 prematurely deliverd children (136 breech and 138 vertex) were attending normal schools About 20 per cent of these children whether born in breech or in vertex presentation had hyperkinesia and/or learning disability The children were educationally retarded to the extent that they had needed to repeat one or more years of schooling and supportive educational assistance had been placed at their disposal Speech disorders occurred in about 5 per cent (Table 4)

All the 1921 mature children (963 breech and 958 vertex) were attending normal schools The frequency of hyperkinesia and learning disabilities was 19 per cent in the breech group but 4 per cent in the vertex group The same figures apply for educational retardation to the extent that supportive educational assistance was needed Reading and writing difficulties occurred in about 25 per cent of the children delivered in breech presentation compared to 10 per cent in the control group Speech disorders were reported for 5 per cent of the breech delivered and 2 per cent of the vertex delivered children (Table 5) When the breech presentations were divided in two groups one of vaginal deliveries and another delivered by cesarean section it was found that 20 per cent of the vaginally but only 1 per cent of the abdominally delivered children had hyperkinesia and/or learning disability Reading and writing difficulties occurred among 28 per cent of the vaginally delivered compared with 1 2 per cent of the children delivered by cesarean section Speech disorders occurred in 5 per cent of vaginal deliveries and in 2 per cent of children delivered by cesarean section Table 6

Table IV *The occurrence of hyperkinetic syndrome learning disability and speech disorders in prematurely delivered infants*

Group	Breech delivery No	Breech delivery %	Vertex delivery No	Vertex delivery %
Hyperkinetic syndrome				
1 Impulsivity	39	[illegible]	35	[illegible]
2 Disorder of attention	36	[illegible]	37	[illegible]
3 Emotional lability	[illegible]	21 3	[illegible]	[illegible]
All three symptoms combined	27	19 9	6	[illegible]
Learning disability				
1 Dyslexia	38	[illegible]	41	[illegible]
2 Dysgraphia	33	[illegible]	[illegible]	[illegible]
3 Dyscalculia	31	[illegible]	30	[illegible]
• All three symptoms combined	30	[illegible]	[illegible]	[illegible]
• *Hyperkinetic syndrome and learning disability combined*	6	19 1	[illegible]	[illegible]
Speech disorders	6	4 4		5 1
All three syndromes combined	1	0 7	1	0
Total number of infants	136		138	

Table V *The occurrence of hyperkinetic syndrome learning disability and speech disorders in term delivered infants*

Group	Breech delivery No	Breech delivery %	Vertex delivery No	Vertex delivery %
Hyperkinetic syndrome				
1 Impulsivity	242	25 1	68	7 1
2 Disorder of attention	241	25 0	57	5 9
3 Emotional lability	236	24 5	61	6 4
All three symptoms combined	178	18 5	36	3 8
Learning disability				
1 Dyslexia	246	25 5	97	10 1
2 Dysgraphia	243	25 2	91	9 5
3 Dyscalculia	245	25 4	94	9 8
All three symptoms combined	181	18 8	39	4 1
Hyperkinetic syndrome and learning disability combined	134	13 9	17	1 8
Speech disorders	47	4 9	19	2 0
All three syndromes combined	23	2 4	6	0 6
Total number of infants	963		958	

There was a marked predominance of females in breech material (60 per cent) which might be explained at least partly by the increased chance of survival of female infants delivered in breech presentation compared with male infants of similar birth weight (3 4) Hyperkinesia and learning disabilities occurred in 25 per cent of the males compared with 15 per cent of the females Table 7

DISCUSSION

Minimal brain dysfunction is one of a number of designations for a common behavioral syndrome affecting shool age children of average intelligence Other terms that have been employed are the hyperkinetic behavior syndrome including short attention span impulsivity and emotional lability and learning disability which can be subdivided into dyslexia dysgraphia and dyscalculia (see Table 8) These terms refer to the same group of children and are interchangeable for practical clinical work Theoretically however the hyperactive behavior disorder is a psychiatric the learning disability syndrome an educational and the MBD syndrome a neurological concept The choice of term depends on various factors such as individual preference area of special interest and the most prominent symptom presented

While the occurrence of MBD is recognized world wide the reported incidence varies between countries The accuracy of the figures is affected by the age of the study material and by differences in interpretation and diagnostic criteria According to Millichap (7) approximately 4 per cent of children under 12 years of age have signs of MBD prevalence figures in the range 5 10 per cent have been reported from various geographical areas (5 6 11) These figures are in good agreement with the incidence of hyperkinesia and/or learning disability found in the group of mature infants delivered in vertex presentation In this investigation the study population has reached a maximum age of 15 years

The figure of 4 per cent should be compared with the frequency of 18 20 per cent in the group of mature children delivered in breech presentation and the same percentage in the group delivered prematurely irrespective of the mode of presentation

Turning to the various categories of disorders one finds that symptoms overlap considerably Peters and co-workers (10) have described for example the group of children with purely hyper active (mainly attentional) disorders 10-15 per cent with pure learning disability and 80-85 per cent with a mixture of both The figures presented in Table 5 are markedly similar

Several reports in the literature (1 7 8 9) indicate that especially hyperkinesia is recognized more commonly in boys than in girls This male predominance might be as high as 4-8 boys for every girl in the affected groups of children The high male preponderance might represent a slower tempo of maturation in the male Girls tend to acquire inhibitory abilities and capacity to sustain attention over a prolonged period of time earlier than boys (13) Focusing on the group of children of to 15 years of age delivered in breech presentation (Table 7) we find a 24 per cent indicence of hyperkinesia among the boys compared to 15 per cent among the girls Looking at the incidence of a combination of hyperkinesia and learning disability the male predominance becomes less marked

Learning requires the integration of a large variety of physiologic and psychologic processes together with the ability to accept a specific set of values as well as the constraints of the class room Thus there are many entities which can lead to hyperactivity disturbed behavior and poor school performance Amongst the major entities discussed in the literature factors such as inappropriate demands on the child incorrect judgement of behaviour by teachers and parents as well as pathological conditions (e g

Table VI *The occurrence of hyperkinetic syndrome learning disability and speech disorders in infants in breech presentation by mode of delivery*

Group	Vaginal delivery		Cesarean section	
	No	%	No	%
Hyperkinetic syndrome				
1 Impulsivity	239	27 6	3	3 1
2 Disorder of attention	239	27 6	2	2 0
3 Emotional lability	233	26 9	3	3 1
All three symptoms combined	176	20 3	2	2 0
Learning disability				
1 Dyslexia	244	28 2	2	2 0
2 Dysgraphia	242	28 0	1	1 0
3 Dyscalculia	244	28 2	1	1 0
All three symptoms combined	180	20 8	1	1 0
• *Hyperkinetic syndrome and learning disability combined*	133	15 4	1	1 0
Speech disorders	45	5 2	2	2 0
• *All three syndromes combined*	23	2 7	—	—
Total number of infants	865		98	

Table VII *The occurrence of hyperkinetic syndrome learning disability and speech disorders in infants delivered in breech presentation by sex of the child*

Group	Males		Females	
	No	%	No	%
Hyperkinetic syndrome				
1 Impulsivity	118	31 0	[illegible]	[illegible]
2 Disorder of attention	123	32 3	118	20 1
3 Emotional lability	109	28 6	127	[illegible]
• All three symptoms combined	92	24 1	86	14 1
Learning disability				
1 Dyslexia	116	30 4	130	[illegible]
2 Dysgraphia	114	[illegible]	[illegible]	[illegible]
3 Dyscalculia	111	29 1	134	23 0
• All three symptoms combined	97	25 5	84	14 4
• *Hyperkinetic syndrome and learning disability combined*	61	16 0	73	12 5
Speech disorders	20	5 2	27	4 6
• *All three syndromes combined*	14	3 7	9	1 5
Total number of infants	963		[illegible]	

epilepsy and brain tumors) must be considered for the differential diagnosis (1) The presence of the hyperkinetic syndrom with attentional disorder and learning disability is suggested mainly by the absence in history and examination of support for other medical and neurological diseases

The care of children with manifest MBD and prob connected with the effect of pharmacological on is the responsibility of pediatricians neu ists and psychiatrists The results of this study however suggest that besides other etiological factors maturity at birth as well as trauma and possibly even periods of asphyxia during delivery play a significant role for the occurrence of MBD It might therefore be concluded that with correct management of the delivery especially in breech presentation the obstetrician can contribute considerably to the prevention of minimal brain dysfunction

DEFINITIONS

The hyperkinetic syndrome is a behavior disorder in children characterized by an unusual degree of motor restlessness (an involuntary and constant overactivity surpassing the normal) and includes impulsivity disorders of attention and emotional lability

Impulsivity An impulsive child is described as doing things on the spur of the moment without thinking and has an inability to delay gratification

Disorder of attention Concentration on a single activity is usually short with frequent shifting from one activity to another poor powers of concentration

Emotional lability The reactions of the child are often almost volcanic in their intensity

Learning disability is an eductional concept distinguishing the underachiever of normal intelligence from the mentally retarded or physically handicapped child It focuses on specific deficits in speech language perception and memory The syndrome comprises terms such as

Dyslexia which signifies the inability to cope with printed and written language

Dysgraphia which is impaired ability to express or execute thoughts by hand wri ing

Dyscalculia which is a term describing difficulty with number concepts

Speech disorders are based on impairments in visual and auditory discrimination and memory The syndrome is characterized by inability of the child to retain sharply outlined verbal configurations

REFERENCES

1 Adler S J & Terry K C Your overactive child normal or not Medcom Inc New York 19[illegible]

2 Alexopoulos K A The importance of breech delivery in the pathogenesis of brain damage End results of a long term follow up Clin Pediatr Vol 12, No 4 (1973) pp 248 249

3 Drillien C M The incidence of mental and physical handicaps in school age children of very low birth weight Pediatrics Vol 39 No 2 (1967) pp 241
4 Fianu S Fetal mortality and morbidity following breech delivery Acta Obstet Gynecol Scand Suppl 56 (1976) pp 71 77
5 Huessy H R Study of the prevalence and therapy of the choreiform syndrome or hyperkinesis in rural Vermont Acta Paedopsuchiatr *34* 130 1967
6 Miller R G Jr Palkes H S & Stewart M A Hyperactive children in suburbans elementary schools Child Psychatry Hum Dev *4* 121 1974
7 Millichap J G Definitions and diagnosis of minimal brain dysfunction *In* Learning disabilities and related disorders Facts and current issues (ed J G Millichap) Year Book Medical Publishers Inc Chicago 1977
8 Millichap J G Learning disabilities and related disorders Facts and current issues Year Book Publishers Inc Chicago 1977
9 Peters J E Davis J S Goolsby C M Clements S D & Hicks T J Physician s Handbook Schreening for MBD CIBA Medical Horizons 1973
10 Peters J E Rommie J S & Dykman R A A special neurological examination of children with learning disabilities Dev Med Child Neurol *17* 63 1975
11 Prechtl H F R & Stemmer C J The choreiform syndrome in children Dev Med Child Neurol *4* 119 1962
12 Sadowski R Staemmler H J Zum Einfluss der Beckenendlagengeburt auf die feistige und körperliche Entwicklung der Kinder Z Geburtsh Perinat 178 (1974) pp 104-110
13 Schain R J Etiology and early manifestations of MBD *In* Learning disabilities and related disorders Facts and current issues (ed J G Millichap) Year Book Medical Publishers Inc Chicago 1977
14 Tenhaeff D Spulak Esser E & Feldmann H U Das lernbehinderte Kind nach Geburt in Beckenendlage Munch Med Wschr 114 (1972) No 37 pp 1565 1569
15 Wender P H Some speculations concerning a possible biochemical basis of M B D Life Sci Vol 14 (1975) pp 1605 1621

Submitted for publication March 17 1978

Stefan Fianu M D
Department of Obstetrics and Gynecology
Sabbatsberg Hospital
Karolinska Institutet
S-113 82 Stockholm
Sweden

Table VI *The occurrence of hyperkinetic syndrome learning disability and speech disorders in infants in breech presentation by mode of delivery*

Group	Vaginal delivery No	Vaginal delivery %	Cesarean section No	Cesarean section %
Hyperkinetic syndrome				
1 *Impulsivity*	239	27 6	3	3 1
2 Disorder of attention	239	27 6	2	2 0
3 Emotional lability	233	26 9	3	3 1
All three symptoms combined	176	20 3	2	2 0
Learning disability				
1 Dyslexia	244	28 2	2	2 0
2 Dysgraphia	242	28 0	1	1 0
3 Dyscalculia	244	28 2	1	1 0
All three symptoms combined	180	20 8	1	1 0
Hyperkinetic syndrome and learning disability combined	133	15 4	1	1 0
Speech disorders	45	5 2	2	2 0
* *All three syndromes combined*	23	2 7	—	—
Total number of infants	865		98	

Table VII *The occurrence of hyperkinetic syndrome learning disability and speech disorders in infants delivered in breech presentation by sex of the child*

Group	Males No	Males %	Females No	Females %
Hyperkinetic syndrome				
1 Impulsivity	118	31 0	1 4	13
2 Disorder of attention	123	32 3	118	20 3
3 Emotional lability	109	28 6	177	21 1
• All three symptoms combined	92	24 1	86	14 1
Learning disability				
1 Dyslexia	116	30 4	130	22 3
2 Dysgraphia	114	29 9	129	22 2
3 Dyscalculia	111	29 1	134	23 0
• All three symptoms combined	97	25 5	84	14 4
Hyperkinetic syndrome and learning disability combined	61	16 0	73	12 5
Speech disorders	20	5 2	27	4 6
All three syndromes combined	14	3 7	9	1 5
Total number of infants	963		958	

epilepsy and brain tumors) must be considered for the differential diagnosis (1) The presence of the hyperkinetic syndrom with attentional disorder and learning disability is suggested mainly by the absence in history and examination of support for other medical and neurological diseases

The care of children with manifest MBD and prob- conrected with the effect of pharmacological ation is the responsibility of pediatricians neu ›gists and psychiatrists The results of this study however suggest that besides other etiological factors maturity at birth as well as trauma and possibly even periods of asphyxia during delivery play a significant role for the occurrence of MBD It might therefore be concluded that with correct management of the delivery especially in breech presentation the obstetrician can contribute considerably to the prevention of minimal brain dysfunction

DEFINITIONS

The hyperkinetic syndrome is a behavior disorder in children characterized by an unusual degree of motor restlessness (an involuntary and constant overactivity surpassing the normal) and includes impulsivity disorders of attention and emotional lability

Impulsivity An impulsive child is described as doing things on the spur of the moment without thinking and has an inability to delay gratification

Disorder of attention Concentration on a single activity is usually short with frequent shifting from one activity to another, poor powers of concentration

Emotional lability The reactions of the child are often almost volcanic in their intensity

Learning disability is an eductional concept distinguishing the underachiever of normal intelligence from the mentally retarded or physically handicapped child It focuses on specific deficits in speech language perception and memory The syndrome comprises terms such as

Dyslexia which signifies the inability to cope with printed and written language

Dysgraphia which is impaired ability to express or execute thoughts by hand wri ing

Dyscalculia which is a term describing difficulty with number concepts

Speech disorders are based on impairments in visual and auditory discrimination and memory The syndrome is characterized by inability of the child to retain sharply outlined verbal configurations

REFERENCES

1 Adler S J & Terry K C Your overactive child normal or not Med om Inc New York 197?
2 Alexopoulos K A The importance of breech delivery in the pathogenesis of brain damage End results of a long term follow up Clin Pediatr Vol 1 N 4 (1973) pp 248 249

Acta Obstet Gynecol Scand 58 301–303 1979

INFERTILITY AND CERVICAL CHLAMYDIA TRACHOMATIS INFECTIONS

J A Paavonen P Saikku E Vesterinen and P Lehtovirta

From the Departments of Obstetrics and Gynecology I II University Central Hospital and the Department of Virology University of Helsinki Helsinki Finland

Abstract Of the 51 women examined for infertility 19 6 per cent were found *Chl trachomatis* culture positive This differs although not significantly from the 9 per cent isolation rate among our general gynecological outpatients The results suggest that *Chl trachomatis* should be considered in women with unexplained infertility

Chlamydiae are intracellular inclusion forming parasites and man is the only known host for *Chlamydia trachomatis* causing trachoma inclusion conjunctivitis lymphogranuloma venereum and genitourinary infections (11) Recent studies indicate that *Chl trachomatis* is a fairly common inhabitant of the female genital tract (3 5 7 9 13) An important question is the possible role of untreated chlamydial infection in female infertility In some animals sterility has been attributed to chlamydial diseases (12) Women with persistent *Chl trachomatis* infection are unlikely to be diagnosed unless isolation of the agent is attempted since distinctive symptoms or signs are not always present (6 7) The aim of this work was to study the possible role of chlamydial genital infection in female infertility

MATERIAL AND METHODS

The subjects were 51 consecutive infertility patients who attended the fertility outpatient clinic in Departments of Obstetrics and Gynecology I II University Central Hospital Helsinki Finland in December 1976 There was no preselection of the patients Only those were excluded who had taken antibiotics or sulphonamides during the last month All the patients had visited this outpatient clinic several times and were examinated carefully concerning etiological factors in infertility Routine tests included basal body temperature (BBT) vaginal smear for hormonal test serum progesterone hysterosalpingography (HSG) post coital test (PCT) and partner s semen analysis

Specimens for chlamydial isolation were collected with sterile cottonwool swabs from endocervix and urethra into 2 SP transport medium (2) further buffered with 0 75 per cent bovine albumin Gentamicin 20 µg/ml was used as antibiotic Specimens were transferred immediately at 4 C and transported the same day to the isolation unit in the same hospital complex where they were stored at −70 C Isolation attempts were done conventionally (1) in irradiated McCoy cells with minor modifications Growth medium was Eagle s minimal essential medium with double amounts of amino acids and vitamins supplemented with 10 per cent fetal calf serum (Gibco) and 1 per cent glucose and gentamicin 20 µg/ml This was used as maintenance medium with additional nystatin 500 units/ml Monolayers were grown onto coverslips 13 mm in diameter in 5 ml Bijou bottles (Sterilin) Samples were centrifuged onto coverslips in a Sorvall ultracentrifuge equipped with a swing out head at 6000 G for one hour at 35 C After incubation for 72 hours in a humidified 5 per cent CO_2 atmosphere the coverslips were fixed with methanol and stained for 15 min with Lugol s solution to demonstrate iodine positive Chl trachomatis inclusions

RESULTS

Of the 51 patients studied 10 (19 6 per cent) excreted Chl trachomatis (Table I) The mean age of the patients was 29 1 years (range 22 to 38) The age distribution of the patients is shown in Table II

The definitions of infertility were similar among chlamydia positive and negative patients (Table III)

No abnormalities of the cervix were observed among chlamydia positive patients In three cases the vaginal smear taken for hormonal test showed inflammatory reaction The distribution of known etiological factors of infertility was rather similar in the two patient groups (table IV) except that the etiology of infertility remained unexplained in 5/10 chlamydia positive patients but in only 7/41 (17 per cent) chlamydia negative patients This difference is however statistically not significant ($\chi^2 = 3\ 19$ $p < 0\ 1$)

DISCUSSION

Little is known of the incidence of chlamydial genital infections in asymptomatic gynecological patients (9

Table I *Recovery of Chlamydia trachomatis from the genital tracts of 51 asymptomatic women attending a gynecological outpatient clinic for infertility*

Result	No	%
Chlamydia positive	10	19 6
Chlamydia negative	41	80 4
Total	51	100 0

Table II *The age distribution of patients*

Age groups	Chlamydia pos	Chlamydia neg	Total
21—25	3	3	6
26—30	4	26	30
31—35	1	11	1
36—38	2	1	3

10) We found a 19 6 per cent isolation rate of Chl trachomatis among 51 female infertility patients This differs ($\chi^2 = 3$ 10 $p < 0$ 1) from the 9 0 per cent isolation rate in our general outpatient population (7)

Chl trachomatis is now recognized as a major cause of nongonococcal and postgonococcal urethritis in men and as a common finding in the genital flora of female patients attending venereal disease clinics as well as of partners of men with the above mentioned diseases (3 4 5 9 13) Our results point to the possible association of Chl trachomatis in some cases of female infertility The underlying mechanism is obscure We found no evidence of chronic salpingitis with tubal occlusions as a causative factor in this series and likewise no pathological results in semen analyses of the partners although nonspecific urethritis is well known to lead occasionly to prostatitis and epididymitis The long term se l a of chronic chlamydial cervicitis are however nknown and infertility may be one symptom of condition This deserves further research with the modern isolation and serology (8) methods developed

REFERENCES

1 Darougar S Kinnison J R & Jones B R Simplified irridated McCoy cell culture for isolation of chlamydiae *In Trachoma and related disorders* (ed R L Nichols) pp 63 70 Excerpta Medica Amsterdam 1971

2 Dunlop E M C Vaughan Jackson J D & Darougar S Chlamydial infection Improved methods of collection of material for culture from the urogenital tract and rectum *Br J Vener Dis 48* 421 1972

3 Hilton A L Richmond S J Milne J D H F & Clarke S K R Chlamydia A in the female genital tract *Br J Vener Dis 50* 1 1974

4 Holmes K K Handsfield H H Wang S P Wentworth B B Turck M Anderson J B & Alexander E R Etiology of nongonococcal urethritis N Engl J Med *292* 1199 1975

5 Oriel J D Powis P A Reeve P M A & Nicol C S Chlamydial infections of the cervix Br J Vener Dis *50* 11 1974

6 Oriel J D Ridgway G L Reeve P Beckingham D C & Owen J The lack of effect of ampicillin plus probenecid given for genital infections with Neisseria gonorrheae on associated infections with Chlamydia trachomatis J Infect Dis *133* 568 1976

7 Paavonen J A Saikku P Vesterinen E B Vartiainen E & Saksela E Genital chlamydial infections in patients attending a gynaecological outpatient clinic Br J Vener Dis *54* 257 1978

8 Saikku P & Paavonen J Single antigen immunofluorescence test for chlamydial antibodies J Clin Microbiol *8* 119 1978

9 Schachter J Hanna L Hill E C Massad S Sheppard C W Conte J E Jr Cohen S N &

Table III *Definitions of infertility and chlamydial isolation results of 51 women*

Infertility	Chlamydia pos No	%	Chlamydia neg No	%	Total No	%
Primary	8	80	34	83	42	82
Secondary	2	20	7	17	9	18

Table IV *Etiology of infertility in 51 women compared with chlamydial isolation results*

Etiology of infertility	Chlamydia pos No	Chlamydia neg No
Endometriosis	1/10	4/41
Polycystic ovaries	0/10	3/41
Ovulatory failure	1/10	15/41
Tubal occlusion	0/9	3/39
PCT negative	3/7	16/33
Partner s semen analysis pathological	3/9	15/3
Unexplained etiology	5/10	/41

Meyer K F Are chlamydial infections the most prevalentvenereal disease? JAMA *231* 1252 1975
10 Schachter J Hill E C King E B Coleman V R Jones P & Meyer K F Chlamydial infections in women with cervical dysplasia Am J Obstet Gynecol *123* 753 1975
11 Schachter J Storz J Tarizzo M L & Bögel K Chlamydiae as agents of human and animal diseases Bull WHO *49* 443 1973
12 Storz J Chlamydia and chlamydia induced diseases Springfield Ill Charles C Thomas 1971
13 Wentworth B B Bonin P Holmes K K Gutman L Wiesner P & Alexander E R Isolation of viruses bacteria and other organisms from venereal disease clinic patients Methodology and problems associated with multiple isolations Health Lab Sci *10* 75 1973

Submitted for publication August 19 1977

J A Paavonen
Department of Obstetrics and Gynecology II
University Central Hospital
Haartmaninkatu 2
00?90 Helsinki
Finland

BOOKS RECEIVED

Andrologie by *Jeno Molnár* and *Ferenc S arvas* Akademiai Kiadó Budapest 1978 (ISBN 963-05 561 X) 199 pages

Endocrinologie prenatale et parturition Edited by *Lise Cédard* and *Claude Sureau* Institut National de la Santé et de la Recherche Médicale Inserm Paris 1978 (ISBN 2 85598 172 7) 315 pages

Endocrine Control in Neoplasia Progress in Cancer Research and Therapy volume 9 Edited by *Rameshwar K Sharma* and *Wayne E Criss* Raven Press New York 1978 (ISBN 0-89004-244-6) 377 pages

Endometrial cancer Edited by *M G Brush R J B King* and *R W Taylor* Bailliere Tindall London 1978 (ISBN 0-702-0713 7) 459 pages

Fetal endocrinology Contributions to Gynecology and Obstetrics volume 5 Edited by *T Zondek* and *L H Zondek* S Karger AG Basel 1979 (ISBN 3 8055 2926-0) 158 pages

Gynekologi by *Knut Bjøro* and *Per Kolst d* Universitetsforlaget Scandinavian University Books Oslo 1979 (ISBN 82 00-07470-2) 327 pages

Haemorrhage Ischaemia and the Perinatal Brain Clinics in Developmental Medicine Nos 69/70 by *Karen E Pape* and *J S Wigglesworth* Spastics International Medical Publications with Heinemann Medical London 1979 (ISBN 0-433-255 0-6) 196 pages Pound sterling 9 50

Human Oocytes and Their Chromosomes by *B M Leber Kallhardt* Springer Verlag KG Berlin 1978 (ISBN 3-540-08879 2) 106 pages US dollars 24 00

Moderne Kontrazeption by *Fritz K Beller* and *Helmut D Böttcher* Georg Thieme Verlag Stuttgart D-7000 Stuttgart 1 Herdweg 63 Postfach 732 West Germany (ISBN 3-13 529501 X) 118 pages

Ovarian Follicular Development and Function Edited by *A Rees Midgley* and *William A Sadler* Raven Press New York 1979 (ISBN 0-89004 186-5) 414 pages

Acta Obstet Gynecol Scand 58 305–307 1979

CASE REPORT

PLASMA ESTRIOL PROGESTERONE CORTISOL PLACENTAL LACTOGEN AND ALPHA FETOPROTEIN IN A PREGNANCY WITH AN ANENCEPHALIC FETUS FOLLOWED FROM THE SEVENTH WEEK TILL TERM

N Sagen M Ulstein I Romslo and K F Støa

From the Department of Obstetrics and Gynecology Department of Clinical Biochemistry and Hormone Laboratory Haukeland sykehus Bergen Norway

Abstract Concentrations of total estriol progesterone cortisol human placental lactogen and alpha fetoprotein were measured in maternal venous plasma at regular intervals from the seventh week of pregnancy until term in a woman with an anencephalic fetus Except for the first trimester during which the values were in the lower normal range the concentration of estriol was constantly subnormal The physiological rise in cortisol levels was absent Progesterone and HPL were both within the low normal range The levels of alpha fetoprotein were transiently raised during the 13th 25th weeks of pregnancy

Recording specific fetal and placental proteins in addition to steroid hormones in a group of arbitrarily selected pregnant women in order to establish normal values we happened to include in our study one case of anencephaly Although such studies recently have been carried out with respect to alpha protein (AFP) (10) this is to our knowledge the first case of anencephaly in which maternal plasma has been examined continually for steroids and HPL throughout pregnancy

METHODS

Starting at the 7th completed week of pregnancy 14 blood samples were taken between 09 00 and 11 30 a m at regular intervals in heparinized tubes from the antecubital vein The samples were centrifuged immediately and stored at 0 C until analyzed Plasma cortisol was measured by competitive protein binding (12) using human third trimester pregnancy plasma as the source of transcortin and Dextran-charcoal suspension for separation of the free and bound steroid

Total plasma estriol assay was carried out on ether extracts of 250 µl plasma following acid hydrolysis and neutralization The method whi h is essentially similar to that described for urine by Anderson and Goebelsman (1) will be described in detail elsewhere (15)

Progesterone was determined essentially as described by Furuyama and Nugent (7) Radioimmunoassay of HPL and AFP was carried out using commercial kits from The Radiochemical Centre Amersham and Dainabot Radioisotope Lab Ltd Tokyo respectively

The procedures for total estriol cortisol progesterone HPL and AFP had between assay variations of 13 7 per cent 11 5 per cent 5 6 per cent 9 8 per cent and 7 3 per cent respectively

CASE REPORT

The patient was a 29 years old gravida II Labor was induced at term by oxytocin and amniotomy and she delivered an anencephalic stillborn fetus weighing 2 500 g and a length 46 cm Autopsy showed anencephalus (microcephalic type) The fetal zone of the adrenal cortex was missing The weight of the placenta was 500 g The analytical resul s are presented in table I During the first 13 weeks of pregnancy the total estriol values (free + conjugated estriol) rose to 2 08 µmol/l (60 ng per 100 ml) plasma which is at the lower limit of the normal range of variation (15) From then onwards the values were abnormally low showing a significant rise from the 31st week until term

Plasma cortisol levels varied between 201 µmol/l and 541 µmol/l (7 3 and 19 6 µg/100 ml) These values showed no significant increase or decrease during pregnancy Plasma progesterone levels rose from 72 µmol/l (22 5 ng/ml) in the 7th week up to about 436 µmol/l (137 ng/ml) in the 37th-40th week

HPL levels were within the normal range (11 14) although below average rising from 0 01 µg/ml at the 7th week of pregnancy to 5 6 µg/ml near term

Serum AFP levels increased from non detectabl amounts at week 7 to a peak of 380 ng/ml at 25 weeks Thereafter the values gradually diminished

Table I *Plasma levels of total estriol progesterone estriol human placental lactogen (HPL) and alpha fetoprotein (AFP) in a pregnant woman with an anencephalic fetus*

Completed weeks of pregnancy	Total estriol (µmol/l)	Cortisol (nmol/l)	Progesterone (nmol/l)	Human placental lactogen (HPL) (µg/ml)	Alpha fetoprotein (ng/ml)
7	2 4	268	71 6	0 01	Non-detectable
13	2 1	541	83 6	0 4	37
17	4 8	213	64 9	1 0	145
21	6 7	541	71 6	1 3	300
25	6 7	431	131 3	2 3	380
28	10 4	466	183 8	3 4	158
31	41 6	287	199 4	4 2	164
33	24 3	293	287 2	4 8	176
35	52 1	293	248 7	5 2	64
36	45 1	262	270 3	5 3	74
37	45 1	215	436 3	5 0	68
38	31 2	221	373 7	4 9	92
39	62 5	248	286 2	5 5	46
40	41 6	201	437 3	5 6	48

DISCUSSION

In accordance with the now well established fact originally documented by Frandsen and Stakemann (6) the present case demonstrates that a pregnancy with an anencephalic fetus having atrophic adrenal cortex is associated with a significantly low production of estriol This finding which is interpreted as being the result of insufficient fetal production of adrenocortical estriol precursors is in agreement with values previously obtained for late pregnancy both urinary and plasma estrogens (5 6)

There was a rather abrupt increase in the estriol levels at the 30th week but since fetal contribution may be consider minimal this might be explained as a pronounced increase in placental aromatase activity

The plasma cortisol values in this case are obviously in contrast to normal pregnancy where increasing levels of cortisol are found (2 3) Although nonprotein bound cortisol has been found to be elevated in normal pregnancy (4) the main cause of the increase in blood cortisol is considered to be an elevation of the concentration and activity of transcortin As the normally increased transcortin activity in pregnancy most certainly is induced by estrogens the absence of an elevation of plasma cortisol can be explained by the abnormally low production of estrogen in the described case

The plasma levels of progesterone are in agreement with the values found in normal pregnant women by Johansson using a competative protein binding technique (9) Systematic progesterone determinations in pregnant women with anencephalic fetuses have apparently not been carried out Recently however Miyakawa *et al* (13) have reported progesterone assays at delivery in maternal plasma and in mixed cord plasma in three cases of anencephaly No differences could be found between the plasma progesterone levels of normal pregnancy and the levels in anencephaly These findings agree with ours and confirm the general opinion originally put forth by Frandsen and Stakemann (6) that fetal contribution of pregnenolone sulphate or cholesterol is not necessary for normal progesterone production (8)

The progesterone values as well as the weight of the placenta indicate that the placenta had developed and functioned normally in the present case Further proof of normal placental function is given by the HPL levels all of which were within the normal range (11 14)

In agreement with results obtained by Leighton et al (10) the peak level of AFP in our case appeared at an abnormally early stage in pregnancy In spite of a number of both false positive and false-negative results reported (10) there seems to be little doubt that findings of abnormally high AFP levels at the 20th 25th week followed by a subsequent decline

give an indication of a neural tube defect of the fetus Corroborated by determinations of plasma estriol AFP assays may therefore present the basis of a screening programme for the early diagnosis of this type of abnormal pregnancy

REFERENCES

1 Anderson D W & Goebelsman U Rapid radioimmunoassay of total urinary oestriol Clin Chem *22* 611 1976
2 Baylis R I S Browne J C M Round B P & Steinbeck A W Plasma 17 hydroxycorticosteroids in pregnancy Lancet 1 62 1955
3 Bro-Rasmussen F Buus O Lundwall F & Trolle D Variations in plasma cortisol during pregnancy delivery and the puerperium Acta Endocrinol (Kbh) *40* 571 1962
4 Burke C W & Roulet F Increased exposure of tissues to cortisol in late pregnancy Br Med J *1* 657 1970
5 Dean L Abell D A & Beischer N A Incidence of anencephaly and other major malformations when oestriol excretion is very low Br Med J *1* 257 1977
6 Frandsen V A & Stakemann G The site of production of oestrogenic hormones in human pregnancy Acta Endocrinol (Kbh) *38* 383 1961
7 Furuyama S & Nugent C A A radioimmunoassay for plasma progesterone Steroid *17* 663 1971
8 Hellig H Lefebvre Y Gattereau D & Bolte E Placental progesterone synthesis in the human The Foeto-Placental Unit ed A Pecile and C Finzi p 152 Amsterdam Excerpta Medica Foundation
9 Johansson E D B Plasma levels of progesterone in pregnancy measured by a rapid competitive protein binding technique Acta Endocrinol (Kbh) *61* 607 1969
10 Leighton P C Gordon Y B Kitau M J Leek A E & Chard T Levels of alpha fetoprotein in maternal blood as a screening test for fetal neuraltube defect Lancet *2* 1012 1975
11 Letchworth A T Boardman R J Bristow C Landon J & Chard T A rapid semi automated method for the measurement of human chorionic somatomammotrophin The normal range in the third trimester and its relation to fetal weight J Obstet Gynecol *78* 54? 1971
12 Murphy B E P Clinical evaluation of urinary cortisol determinations by competitive proteinbinding radioassay J Clin Endocrinol Metab *28* 343 1968
13 Miyakawa I Ikeda I Nakayama M & Maeyama M Plasma concentrations of cortisol progesterone and unconjugated oestradiol and oestriol in women with live anancephalic foetuses before during and after labour J Endocrinol Metab *69* 291 1976
14 Niven P A R Landon J & Chard T Placental lactogen levels as guide to outcome of threatened abortion Br Med J *3* 799 1972
15 Sagen N Støa K F & Ulstein M To be published
16 Svendsen R & Sørensen B The plasma concentration of unconjugated oesterone and 17 beta-oestradiol during the normal menstrual cycle Acta Endocrinol (Kbh) *47* 245 1964

Submitted for publication June 7 1977

M Ulstein M D
Department of Obstetrics and Gynecology
N 5016 Haukeland sykehus
Bergen
Norway

BOOKS RECEIVED

Progress in Cancer Research and Therapy volume 9 Endocrine Control in Neoplasia Edited by *Rameshwark K Sharma* and *Wayne E Criss* Raven Press 1140 Avenue of the Americas New York N Y 10036 1978 (ISBN 0-89004-244-6) 377 pages

Real Time Ultrasound in Perinatal Medicine Contributions to Gynecology and Obstetrics volume 6 Edited by *R Chef* in cooperation with *A Minkowski S Levi G S Dawes* and *A M Rudolph* S Karger AG Basel 1979 (ISBN 3 8055 2976-7) 159 pages Sw Fr 79 U S dollars 47 50

Recent advances in ultrasound diagnosis Proceedings of the International Symposium on Recent Advances in Ultrasound Diagnosis Dubrovnik October 10-15 1977 Editor *Asim Kurjak* Excerpta Medica Amsterdam 1978 (ISBN 0-444-90022 5) 330 pages

Stomach Cancer UICC Technical Report Series [illegible] 34 A Series of Workshops on the biology of [illegible] Cancer report No 6 Edited by *D W Piper* UICC Geneva 1978 (ISBN 92 9018-034-X) 138 pages Sw Fr [illegible]

Synopsis of Obstetrics 10th edition by *Eugene C S[illegible] berg* The C V Mosby Company St Louis 1978 (ISBN [illegible] 8016-3318-4) 644 pages US dollars 17 50

Trauma in pregnancy by *Herbert J Buchsbaum* W B Saunders Company England 1979 (ISBN 0-7216-21[illegible]) 308 pages Pound sterling 15 75

Acta Obstet Gynecol Scand 58 309–312 1979

CASE REPORT

X/X TRANSLOCATION AND TURNER S SYNDROME IN A WOMAN WITH CLIMACTERIUM PRAECOX

Johannes Nielsen Erik Kristoffersen and Akira Homma

From the Cytogenetic Laboratory Århus Psychiatric Hospital Risskov and the Department of Obstetrics and Gynecology Centralsygehuset Herning Denmark

Abstract A woman with X/X tran location is presented and the association between the different types of X/X translocation and Turner s syndrome as well as the question of menstruations and fertility in women with Turner s syn drome are discussed It is conclud d that streak gonads should most probably not be included in the definition of Turner s syndrome

Previous cases of X/X translocations have been published by Sinha & Nora (17) Disteche *et al* (5) van den Berghe *et al* (1) Therman *et al* (20) Kim *et al* (9) de la Chapelle & Steenstrand (3) Ruthner & Golob (15) and Sinha *et al* (18) (Table I)

We have studied a woman with an X/X transloca tion of a type not previously described and the pres ent paper also deals with the association between the different types of X/X translocation and Turner s syndrome as well as with the question of fertility in women with Turner s syndrome

CASE HISTORY

A 36-year old woman from Turkey was referred to the gynecological department at Herning Centralsygehus for secondary amenorrhea from the age of 29 She had had nor mal menstruations from the age of 10 to 24 and oligomenor rhea from 24 to 29 She never developed any climacterial symptoms

She had otherwise always been physically and mentally healthy She is married but has no children She is illiterate and not able to speak any other language than Turkish

Physical examination Physical examination shows a 138 cm tall woman in good health with a normal feminine pheno-type very scanty axillary and pubic hair growth but other wise no signs of Turner s syndrome and no physical abnor malities

Gynecological examination shows a normal vagina and uterus of average size and normal shape

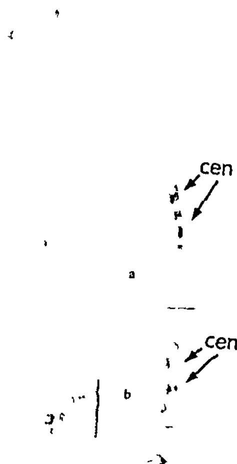
Laboratory examinations Hormone analysis revealed a slight decrease in urinary excretion of androsterone etio-cholanolone and 11 ketosteroids while the concentration of the rest of the steroids was within the normal range There was however also low excretion of estrogens (4 micro-grams per 24 hours) and pituitary gonadotrophins were be low 3 m u per 24 hours Due to these results which indi cated hypogonadism as a possible cause of the secondary amenorrhea treatment with *humegone* followed by treat ment with *physex* was given for three months in increasing doses No menstruations occurred during this treatment and judged from the pregnandiol concentrations no ovula tion took place This lead to the assumption of the presence of ovarian dysgenesis or agenesis and laparoscopy was con sequently performed This examination showed a small atrophical ovary on the left side and no ovary on the right side but otherwise normal conditions Biopsy from the ova ries showed ovary tissue with fibroses but no primordial follicles no Graafian follicles no cysts no luteal corpora or corpora albicantes

Psychiatric examination P ychiatric examination was diffi cult due to lack of a common language for patient and inter viewer but the patient appeared to be of normal intelli gence she was friendly cooperative but somewhat anxious She was of neutral mood and had no signs of mental ill ness

Cytogenetic examination Cytogenetic examination of lymphocytes in BUDR and C staining showed the karyotype 45 X/46 X t(X X) (Xpter–Xcen Xp 22–Xqter) Five of 217 cells from lymphocyte cultures had 45 X (2 3 per cent) with one active X the rest had 46 chromosomes with the above mentioned X/X translocation The large X is most probably derived from translocation between two X chromosomes in a triple X cell line with break of one X at p22 and of the other at the centromere region which has lost its centromere capacity and has been translocated onto the break at p22 of the other X-chromosome with loss of the long arms (Figs 1 and 2)

The other possibility would be a duplication of the major part of the short arms of one X with karyotype 46 X dup (X) (Xp22 Xcen)

Chromosome examination of fibroblast cell cultures (13 cells) as well as cultures from ovary tissue with analysis of 11 cells showed 46 chromosomes one normal X and one X/X translocation as found in lymphocyte cultures but in fibroblast and o ary tissue cultures no cells with 45 X were found



Karyotype
46 X t(X X)(Xpter→Xcen Xp22→Xqter)
DR Acridine Orange stained normal active X and inactive translocation X
b C stained translocation X chromosomes

Fig 2 a Normal X-chromatin from a woman with 46 XX b Large elongated X-chromatin from proband with karyotype 45 X/46 X t(X X)(Xpter→Xcen Xp22→Xqter)

among the live born children could be associated with premature ovarian aging (Talbert (19) and Reyes *et al* (14)) but it might also to a certain extent be due to selection of material as the finding of an abnormal fetus or child in some cases might have been the event which led to diagnosis of the mother

The previous two cases with 46 X t(X X) (p22p22) in all cells described by Disteche *et al* (5) and de la Chapelle & Steenstrand (3) both had primary amenorrhea and short stature and one had cubitus valgus which indicates some loss of short arm material in the process of X/X translocation

The two cases of X/X translocation with p/q or q/q translocation described by Therman *et al* (20) and Laurent *et al* (10) had no signs of Turner s syndrome but one had primary amenorrhea and the other had oligomenorrhea

These findings further support previous findings indicating that short stature and Turner stigmata are caused by lack of some short arm X material while lack of long arm X material may lead to primary amenorrhea without short stature and with no definite Turner stigmata

The case presented had 2 per cent cells with 45 X in lymphocytes but otherwise an X/X translocation with at least one complete short arm X and one complete long arm X Her short stature and scanty pubic and axillary hair growth as well as ovarian dysgenesis are most probably due to the lack of one X chromosome in 2 per cent of cells which was found in lymphocyte cultures and not due to the X/X translocation

Sing and Carr (16) found that the gonads of early 45 X embryos appear to be normal but during fetal life and up till puberty or in a few cases much later, the germ cells degenerate and the typical Turner streak gonads develop

In infants with Turner s syndrome some investigators have however found clusters of germ cells or even premordial follicles (Bore (2) Conen & Glass (4) and Frøland *et al* (7))

The total loss of germ cells and translocation of the Turner ovaries to streak gonads may in cases with a 46 XX or 47 XXX cell line take up to 20-30 years as in the present patient who had menstruations until the age of 29 One of the patients previously studied by us with karyotype 45 X/46 XX/47 XXX had menstruations from the age of 16 to the age of 34

Due to the above mentioned findings streak gonads should most probably not be included in the definition of Turner s syndrome as also stressed by Philip & Sele (13)

Table I *X/X translocations*

Authors	Karyotype	Clinical signs
Distèche *et al* (1972)	46 X +t (X X) (p22 p22)	A 15 year-old girl with primary amenorrhea short stature infantile external genitalia and uterus Cubitus valgus and slight Madelung s deformity of both elbows and mental retardation
Van den Berghe *et al* (1973)	45 X/46 X +t (Xq Xp)	A 14-year-old girl of normal stature with short neck slight webbing of the neck high palate speech difficulties hypertelorism A rather square trunk with widely spaced nipples and cubitus valgus No secondary sex characteristics Normal intellegence but described as doing poorly at school
de la Chapelle & Steenstrand (1974)	46 X +t (X X) (p22 p22)	A 60-year-old female 154 cm tall with primary amenorrhea and no other signs of Turner s syndrome
Kim *et al* (1974)	46 X +t (X X) (p22 q13)	A 16-year-old girl with secondary amenorrhea short stature low hair line widely spaced nipples cubitus valgus short fourth metacarpals no secondary sex characteristics Normal intelligence
Kim *et al* (1974)	45 X/46 X +t (X X) (p22 q13)	A 34-year-old woman with secondary amenorrhea short and obese of stature Slightly increased carrying angles and short fourth and fifth metacarpals Normal secondary sex characteristics Normal intelligence
Ruthner & Golob (1974)	45 X/46 X +t (X X) (p22 p22)	A 25 year-old woman with primary amenorrhea and short stature Low set ears a few pigmented nevi and shield chest Normal secondary sex characteristics
Terman *et al* (1974)	46 X +t (X X) ? (q28 q28)	A 21 year-old girl with primary amenorrhea tall stature (182 cm tall) Minor external ear aberrations No development of secondary sex characteristics infantile external genitalia
Laurent *et al* (1975)	46 X +t (X X) (p22 q12) 47 XY +der t (X X) (p22 q12) mat	No signs of Turner s syndrome but oligomenorrhea A boy with signs of Klinefelter s syndrome
Wagenbichler *et al* (1975)	45 X/46 X +t (X X) (q26 p11)	An 8 year old girl with short stature congenital heart aberration but otherwise no signs of Turner s syndrome

DISCUSSION

The translocation X/X chromosome had only one functioning centromere as has also been found in previously published cases of X/X translocation This is in accordance with the suggestion by de la Chapelle & Steenstrand (3) that only one of the centromeres in a translocation between two chromosomes retains its kinetochore functions

If the classification of 45 X is based on a thorough chromosome examination and analysis of at least 50 cells from lymphocyte as well as fibroblast cultures it is doubtful that the frequency of spontaneous menstruations in this group of Turner s syndrome is but a few per cent The frequency of spontaneous menstruations among those with a 46 XX or 47 XXX cell line will most probably be approximately 20 per cent as predicted by Ferguson Smith (6) in 1965 and found in recent studies of large groups of women with Turner s syndrome by among others Palmer & Reichmann (12) and Nielsen *et al* (11)

Recent literature surveys by Gilboa & Rosenberg (8) Reyes *et al* (14) and Nielsen *et al* (11) reveal seven pregnancies and five live births in five females with karyotype 45 X but not all of them had had a thorough cytogenetic examination and some might have chromosome mosaicism Philip & Sele (13) presented a woman with two pregnancies and 45 X in all 203 cells from lymphocytes fibroblasts and both ovaries There are however reports of 47 pregnancies in 17 women with a cell line of 45 X as well as a cell line of 46 XX and/or 47 XXX Among all 54 pregnancies there were 15 spontaneous abortions (28 per cent) 3 malformed fetuses among 4 stillbirths Twelve of the 36 live born children (33 per cent) had some physical or mental abnormalities 8 (22 per cent) had chromosome abnormalities and of those were 3 with Down s syndrome (8 per cent) and 5 with a 45 X cell line (13 per cent)

The high frequency of abortions (28 per cent) still births (8 per cent) and Down s syndrome (8 per cent)

ACKNOWLEDGEMENT

We are grateful to Dr Gert Bruun Petersen Institute of Human Genetics University of Århus for making chromosome examination of fibroblast and ovarian tissue cultures

REFERENCES

1 Berghe H van den Fryns J P & Soyez C X/X translocation in a patient with Turner syndrome Hum Genet *20* 377 1973
2 Bore K E Gonadal dysgenesis in a newborn with XO karyotype Am J Dis Child *120* 363 1970
3 Chapelle A de la & Steenstrand K Dicentric human X chromosomes Hereditas *76* 259 1974
4 Conen P E & Glass I Turner s syndrome in the new born J Clin Endocr *23* 1 1963
5 Distèche C Hagemeijer A Frederic J & Prog neaux D An abnormal large human chromosome identified as an end to-end fusion of two X s by com bined results of the new banding techniques and microdensitometry Clin Genet *3* 388 1972
6 Ferguson Smith M A Karyotype phenotype correla tions in gonadal dysgenesis and their bearing on the pathogenesis of malformations J Med Genet *2* 14? 1965
7 Frøland A Zykke A & Zachau Christiansen B A micromethod for chromosome analysis in peripheral blood culture Lancet *II* 1?81 196?
8 Gilboa Y & Rosenberg T Typical Turner s syndrome with 45 XO karyotype and normal menstruation Helv Paediat Acta *30* 81 1975
9 Kim H J Hsu L Y F & Hirschhorn K Familial X/X translocation t(X X) (p? q13) Cytogenet Cell Genet *13* 454 1974
urent C Biemont M Cl & Dutrillaux B Sur atre nouveaux cas de translocation du chromosome chez l homme Hum Genet *26* 35 1975
Nielsen J Nyborg H & Dahl G Turner s syndrome A psychiatri psychological study of 45 women with Turner s syndrome compared with their sisters and women with normal karyotypes [illegible] tion and primary amenorrhea Acta Ju[illegible] Medicine Series 21 Århus 1977
12 Palmer C G & Reichmann A Chromosomal [illegible] clinical findings in 110 females with Turner s [illegible] me Hum Genet *35* 35 1976
13 Philip J & Sele V 45 XO Turner s syndrome [illegible] out evidence of mosaicism in a patient with two [illegible] nancies Acta Obstet Gynecol Scand *55* ?83 1976
14 Reyes F I Koh K S & Faiman C Fer[illegible] women with gonadal dysgenesis Am J Obstet Gyne[illegible] *1?6* 668 1976
15 Ruthner U & Golob E Fusion of the short arms [illegible] one X chromosome in a patient with gonadal dysgene sis Hum Genet *24* 159 1974
16 Sing R P & Carr D H The anatomy and h[illegible] of XO human embryos and fetuses Anat Rec *15*[illegible] 1966
17 Sinha A K & Nora J J Evidence for X/X chromo some translocation in humans Ann Hum Gene (Lond) *33* 117 1969
18 Sinha A K Pathak S & Nora J J Fusion of t[illegible] apparantly intact human X chromosomes Hum Gene *32* 295 1976
19 Talbert B Effect of maternal age on reproduc[illegible] capacity Am J Obstet Gynecol *10* 451 1968
20 Therman E Sarto G E & Patau K Center for Bar body condensation on the proximal part of the human Xq A hypothesis Chromosoma (Berl) *44* 361 19[illegible]
21 Wagenbichler P Frisch H & Schnedl W Ein Fa[illegible] von X/X Translokation t(X X) (q 6 p11) Klin Pä[illegible] *187* 533 1975

Submitted for publication September 1 1977

Johannes Nielsen
Cytogenetic Laboratory
Århus Psychiatric Hospital
DK 8240 Risskov
Denmark

Acta Obstet Gynecol Scand 58 313–315 1979

CASE REPORT

THE ROLE OF FETAL MOVEMENTS ASSESSMENT IN CASES OF SEVERE RH IMMUNIZED PATIENTS

E Sadovsky N Laufer and Y Beyth

From the High Risk Pregnancy Unit Department of Obstetrics and Gynecology
Hadassah University Hospital Jerusalem Israel

Abstract Two cases of severe Rh immunization are presented The obstetric history maternal serum anti D titre amniotic fluid spectrophotometric evaluation amniography and ultrasound placentography suggest the diagnosis of hydrops fetalis The reduction of fetal movements until cessation in the presence of an audible fetal heart point to a severely distressed fetus and impending death thus providing additional data confirming the diagnosis of hydrops fetalis The importance of diagnosed hydrops fetalis lies in the fact that most authors agree that in these cases treatment of the fetus should not be attempted

The introduction of anti D immunoglobulin G has considerably lowered the incidence of Rh immunization Yet despite the expansion of programs for the prevention of Rh immunization a few cases are still encountered the majority of which are severely affected since they belong to the pre anti D era or have been sensitized by Rh positive transfusions or injections

In cases of Rh immunization the most useful way to assess the severity of the disease is by serial spectrophotometric examinations of the amniotic fluid at a wavelength of 450 mu Methods have been devised by Liley (6) and Robertson (12) providing simple guide lines for management

Most authors (Percival (9) Pritchard and Mac Donald (10) Bishop *et al* (1) Bowes (2) Fong *et al* (3)) agree that in severe cases of Rh immunization with hydrops fetalis it is useless to transfuse the fetuses intrauterinely or to induce delivery immediately because the affected hydropic fetus has a poor chance of survival Death in utero is common and infants who survive delivery present problems which are likely to become lethal during the early neonatal period in spite of exchange transfusion

A different approach has been advocated by Friesen (4) who claims some success in cases of hydrops fetalis his experience however has not been substantiated by other authors

As intrauterine transfusion has some complications (Friesen (4) Reynolds (11)) and premature delivery in these cases sometimes requires cesarean section it is important to estimate the severity of the disease and to diagnose the cases of hydrops fetalis so as to exclude them from other cases Rh immunization The ability to diagnose hydrops in utero may influence management and certainly ensures that the mother be given a realistic prognosis (Gordon (5)) Hydrops fetalis may be suspected when the history of the women reveals several Rh immunization pregnancies with jaundice newborns and repeated exchange transfusions The amniotic fluid analysis will reveal high values on spectrophotometric analysis however considerable overlap exists between the moderately affected infant and the hydropic one Amniography with Pantopaque will reveal thickness of the subcutaneous tissue of the scalp due to edema and Buddha positon of the fetus because of ascites in the fetal abdomen It is sometimes possible to distinguish by ultrasonic technique the thickness and density of the hydropic placenta (Gordon (5)) However all these aids to the diagnosis of fetal hydrops are sometimes fallible (Friesen (4))

It seems that additional parameters for the diagnosis of hydrops fetalis will be of advantage to the management of these cases

Recently there has been increasing interest in the observation of fetal activity in the evaluation of fetal well being and distress (Mathews (7) Sadovsky and Yaffe (13) Pearson and Weaver (8)) In high risk pregnancy pronounced reduction followed by cessation of fetal movements (F M) while heart sounds are still audible may indicate severe fetal distress and impending death (Sadovsky *et al* (14))



Fig 1 Ultrasound placentography demonstrating a very thick posterior placenta. Maximal thickness 8 cm. Midline longitudinal section

Gordon (5) has already pointed out that hydrops fetalis is most frequently associated with diminished fetal activity It appears to us that in cases of Rh immunization when fetal hydrops is suspected according to the above mentioned diagnostic data the reduction of fetal movement provide an important additional tool suggesting a severely distressed fetus and impending death In these cases neither intrauterine transfusion nor immediate induction of labor be undertaken

The following two cases of severe Rh immunization stress the value of fetal movement assessment in confirming the diagnosis of hydrops fetalis

CASE REPORTS

Case no 1 K B an A Rh negative women aged 31 gravida 3 para 2 was referred to the hospital at the 33rd week of the third pregnancy for evaluation of fetal state In her youth she had received repeated intramuscular injections of blood Her first pregnancy resulted in a jaundiced newborn due to Rh immunization who survived after an exchange transfusion The second pregnancy again resulted in a jaundice infant who died in spite of two exchange transfusions The Δ OD at 450 mu was excessively high 1 070 Fetography revealed a fetus with a large abdomen Buddha position and thick subcutaneous edema over the scalp suggesting hydrops fetalis Within a few days the fetal movements markedly decreased while the fetal heart was audible Two days later she delivered spontaneously a live hydropic infant weighing 1 000 g with an edematous placenta of 800 g The newborn died after several minutes

Case no 2 Z Y a B Rh negative patient aged 31 gravida 9 para 7 and mother of four children was admitted to the hospital during the 30th week of her ninth pregnancy because of increasing Rh antibody titre Her first and second pregnancies resulted in normal term deliveries the newborns were normal without jaundice Her third pregnancy pregnancy terminated in the 8th month with a stillbirth due to abruptio placenta Her fourth pregnancy and delivery were normal The newborn s weight was 4 000 g with slight jaundice no exchange transfusion was needed The fifth and sixth pregnancies terminated in spontaneous abortions in the third month Her seventh pregnancy resulted a term delivery of a 3 900 g infant in another hospital The infant was jaundiced but no exchange transfusion was performed and the newborn died after 24 h In the eight pregnancy intrauterine blood transfusion in the eight month was performed delivery was normal resulting in a live 3 500 g newborn Two exchange transfusions were performed

In her present pregnancy the titre of anti D antibodies in the Indirect Coombs test during the 30th week was 1 256 Amniocenthesis revealed a deep yel-

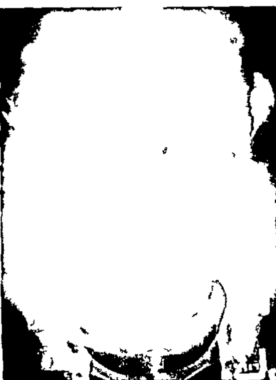


Fig 2 Fetography Fetus demonstrated in breech presentation Note the increased fetal scalp thickness and the protruding abdomen

low tinted amniotic fluid with a △ OD value of 1 120 at 450 mu Ultrasound scanning showed the fetus to be in a breech presentation with a very thick posteriorly located placenta (fig 1) the subcutaneous tissue over the scalp was edematous Fetography with Pantopaque revealed the fetus in Buddha position and confirmed the thickness of subcutaneous tissue over the scalp (fig 2) In additon to these signs of hydrops fetalis the woman claimed that fetal movements were reduced until cessation Fetal heartbeats were heard The reduction in fetal movement pointed to a severely distressed fetus and impending death Two days after cessation of movements the fetal heartbeats were not audible and a day later she delivered spontaneously a 2 330 g hydropic infant with a placenta weighing 1 960 g

COMMENTS

These two cases of Rh immunization were suspected to be hydrops fetalis according to the history of previous pregnancies the high value of △ OD at 450 mu edematous subcutaneous tissue ascites of the abdomen and a thick edematous placenta as was shown in amniography and ultrasound scanning The reduction in fetal movements points to a severely distressed fetus and impending death further confirming the diagnosis of hydrops fetalis

These cases stress the importance of assessing fetal movements in the management of severe Rh immunization cases which are suspected to be hydrops fetalis

REFERENCES

1 Bishop E H Webber L L & Israel S L Intrauterine Transfusion a Second and Critical Look Am J Obstet Gynecol *99* 615 1967
2 Bowes W A Intrauterine Transfusion Indications and Results Clin Obstet Gynecol *14* 561 1971
3 Fong S W Margolis A J Westberg J A & Johnson P Intrauterine Transfusion Fetal Outcome and Complications Pediatrics *45* 576 1970
4 Friesen R F Complications of Intrauterine Transfusion Clin Obstet Gynecol *14* 572 1971
5 Gordon H G The Diagnosis of Hydrops Fetalis Clin Obstet Gynecol *14* 548 1971
6 Liley A W Liquor Amnii Analysis in the Management of the Pregnancy complicated by Rhesus sensitization Am J Obstet Gynecol *82* 1358 1961
7 Mathews D D Measuring Placental Function Br Med J *1* 439 1972
8 Pearson J F & Weaver J B Fetal Activity and Well being an Evauation Br Med J *1* 1305 1976
9 Percival R Holland and Brews Manual of Obstetrics 13th edition Churchill London p 802 1969
10 Pritchard J A & MacDonald P C The Williams Obstetrics 15th edition Appleton-Century Crofts New York p .09 1976
11 Reynolds J W The use of drugs in influencing human fetal metaboli m Clin Obstet Gynecl *17* 395 1974
12 Robertson J G Management of Patients with Rh Isoimmunization Based on Amniotic Fluid Examination Am J Obstet Gynecol *103* 713 1969
13 Sadovsky E & Yaffe H Daily Fetal Movement Recording and Fetal Prognosis Obstet Gynecol *41* 845 1973
14 Sadovsky E Yaffe H & Polishuk W Z Fetal Movement Monitoring in Normal and Pathological Pregnancy International Journal of Gynecology and Obstetrics *12* 75 1974

Sumitted for publication December 15 1977

Eliahu Sadovsky
Department of Obstetrics and Gynecology
Hadassah University Hospital
Jerusalem
Israel

Acta Obstet Gynecol Scand 58 317–319 1979

CASE REPORT

MATERNAL SEPSIS UTERINE RUPTURE AND COAGULOPATHY COMPLICATING CERVICAL CERCLAGE

Bo S Lindberg

From the Department of Obstetrics and Gynecology County Hospital
Västerås Sweden

Abstract A previously healthy woman with a Shirodkar cerclage for cervical incompetence had a spontaneous rupture of the membranes at the 37th week of pregnancy Three days later after a short period of weak labor pains she developed a severe sepsis uterine rupture and coagulopathy leading to renal failure β hemolytic streptococcus group B and peptostreptococcous could be cultured from the amniotic fluid immediately after rupture of the membranes and from the uterus and placenta

Cerclage of the incompetent cervical os is a common procedure in obstetrics It is rarely followed by complications but sometimes hemorrhage recurrent false labor accidental rupture of the membranes fever due to sepsis and even maternal death is encountered (5 6)

In this report a case of maternal sepsis myometritis with uterine rupture and coagulopathy complicating a cervical cerclage is presented

CASE REPORT

M L G was a 31 years old gravida IV para II including one spontaneous abortion at the 20th week of pregnancy and two preterm deliveries Her last baby with a birthweight of 1 600 g had cerebral palsy In the 15th week of the present pregnancy cervical cerclage was performed because of cervical incompetence The pregnancy was then uneventful until the 37th week when spontaneous rupture of membranes occurred The suture was removed and a swab taken from the cervix for bacterial culture Cardiotocographic assessment showed a normal fetal heart rate but no contractions Three days later in the morning the patient complained of pain She admitted that she had experienced labor pains for a few hours in the night but had not told the midwife The uterus and her abdomen were tender on examination and the amniotic fluid had a foul smell her temperature was 37 C and CTG showed repeated late decelerations The cervical os was only two cms dilated An emergency lower segment cesarean section was performed

A boy weighing 2 900 g was extracted with an Apgar score of three at one minute and nine at five minutes After an initial sepsis the neonatal period was uneventful At the age of one month the baby was found dead in his bed at home Autopsy failed to reveal anything but sudden infant death without obvious reason

At the operation placenta was found to be meconium stained and the uterus was flaccid with heavy bleeding A rupture of the lower posterior segment of the uterus was noted Due to the heavy bleeding a subtotal hysterectomy had to be performed During the operation the patient started to bleed from the abdominal wall infusion sites and several other places Her blood pressure was sometimes unrecordable Tranexamic acid fresh blood steroids and antibiotics were given Her trombocytes were low and the bleeding time prolonged Post operatively the bleeding from wound edges drains and subcutaneous tissues continued for some days She then became anuric and this has persisted She has been dialysed and is awaiting renal transplantation

After the operation the results from the bacteriological culture taken at the time of admission were obtained β hemolytic streptococcus group B and peptostreptococcous were isolated from the amniotic fluid The same bacteria were found in the placenta Microscopic examination of the uterus revealed myometritis and necrosis of the uterus wall at the site of the rupture

DISCUSSION

Uterine rupture in the third trimester is an uncommon phenomenon in modern obstetrics The frequency varies in different reports from 1 93 (based on selected series from Uganda (11) to 1 4908 (14) Most *rupture* are traumatic resulting from scars following cesarean section or are caused by obstruction (10 14)

The uterine contractions in this patient cannot have been particularly strong or lasted for many hours as she was regularly attended by the staff during the night In spite of this the uterine wall was ruptured This must have been as a result of the inflammatory myometritis with necrosis of the uterine wall Inflammation in the myometrial tissue with necrosis is a very uncommon cause of rupture of the corpus uteri but it has been reported in older text books (13) The infection was caused by β hemolytic streptococcous group B and peptostreptococcous which were also cultured from the vagina and cervix immediately after rupture of the membranes

Group B β hemolytic streptococci has been reported to be a cause of preterm delivery and perinatal mortality (7 1) Blanc (2) has pointed out that antenatal bacterial infection is usually the result of ascending rather than hematogenous spread of *microorganisms* β hemolytic streptococcous group B in the cervix is fairly common in pregnant women In some cases possibly due to low immunological [illegible]ance the bacteria cause an inflammatory [illegible]ionitis followed by rupture of the mem[illegible] and an ascending infection The cerclage [illegible]terial might act as a foreing body with enhancement of the inflammatory reaction

After the introducton of antibiotics these were used prophylactically in cases of premature rupture of the membranes The initial enthusiasm however soon disappeared and double blind studies have failed to show any advantage of prophylactic treatment (8) It is recommended to take a cervical swab for bacteriological culture and sensitivity tests as soon as the patient is admitted to hospital It is then possible to identify the causal agent and treat with the appropriate antibiotics as soon as signs of infection appear Unfortunately in the present case the development of severe disease was so silent and rapid that adequate antibiotic therapy was not administered soon enough

Treatment of premature rupture of the membranes has long been a subject of controversy Some authors (9) consider that the risk of infection is slight and the advantage of continuing the pregnancy u[illegible]til the fe[illegible] is more mature is great Others (3) propo[illegible] an a[illegible] management with induction of labor within [illegible]

It is not possible to make a clear-cut d[illegible] the exact cause of the shock and the acute re[illegible] failure in this patient Bacterial endotoxins relea[illegible] on disintegration of the cells or exotoxins forme[illegible] some strains of bacteria may produce several e[illegible] on the tissues such as hemolysis muscle [illegible] kidney damage and activation of the fibr[illegible] system In addition hypovolemia with ensuing [illegible] compromisis the renal circulation and might be a co[illegible]tributory cause to the development of acute tu[illegible] necrosis or renal cortical necrosis On reviewing a[illegible]ticles on septic shock and acute renal failure (4 1[illegible] there seems to be general agreement on the pri[illegible] of treatment Replacement of fluid loss [illegible] blood antibiotic cover in adequate dosage a[illegible]d base[illegible] on sensitivity tests and removal of *the infective fo*[illegible] which might include hysterectomy Hystere[illegible] should be resorted to without delay *in the seriously* [illegible] patient particulary in the situation where there [illegible]ficulty in stabilizing the blood pressure and re[illegible] failure supervenes secondary to infection

Cervical cerclage for the incompetent os has sa[illegible] many thousands of infants lives during the la[illegible] decades The complications are few and severe co[illegible]plications such as occurred in the present case a[illegible]tremely rare Experiences of this kind however a[illegible] very educational and should alert the obstetricia[illegible] observe patients with cerclage and premature rup[illegible] of the membranes carefully and be prepared *to* [illegible]tervene at an early stage if complications arise

REFERENCES

1 Berg T Hallander H O Nathorst Windahl G Nordlander J M Groups B beta hemolytic [illegible]tococci as an important cause of perinatal mor[illegible] Scand J Infect Dis 9 19 1977
2 Blanc W A Pathways of fetal and early neo[illegible] infection J Pediatr 59 473 1961
3 Burchell R C *In* Controversy in Obstetrics [illegible] Gynecology (eds D E Reid and T C Barton) [illegible] W B Saunders Philadelphia 1969
4 Douglas G W *In* Controversy in Obstetrics [illegible] Gynecology (eds D E Reid and T C Barton) [illegible] W B Saunders Philadelphia 1969
5 Durn L J Robinson J C & Steer C M [illegible] death following suture of incompetent cervix [illegible] pregnancy Am J Obstet Gynecol [illegible] 33[illegible] 19[illegible]9
6 *Heineman M K Targ C K & Kramer F* [illegible] Placental bacteremia and maternal se[illegible] Shirodkar procedure Am J Obstet Gynecol [illegible] 197[illegible]

7 Hood M Janney A & Dameron G Beta hemolytic streptococcus group B associated with problems of the perinatal period Am J Obstet Gynecol *82* 809 1961
8 Lebherz T B Hellman L P Madding R Anctil A & Arje S L Double blind study of premature rupture of the membranes Am J Obstet Gynecol *87* 218 1963
9 Lebherz T B & Austin J A *In* Controversy in Obstetrics and Gynecology (eds D E Reid and T C Burton) p 37 W B Saunders Philadelphia 1969
10 Palerme G R & Friedman E A Rupture of the gravid uterus in the third trimester Am J Obstet Gynecol *94* 571 1966
11 Rendle Short C W Rupture of the gravid uterus in Uganda Am J Obstet Gynecol *79* 1114 1960
12 Russel K P *In* Controversy in Obstetrics and Gynecology (eds D E Reid and T C Burton) p 277 W B Saunders Philadelphia 1969
13 Seitz L & Amreich A L Biologie und Pathologie des Weibes Verlag Urban & Schwarzenberg Berlin Band IV p 488 1953
14 Åstedt B Rupture of the uterus in Swedish departments of obstetrics 1956-1961 Acta Obstet Gynecol Scand *46* 168 1967

Submitted for publication November 14 1977

Bo S Lindberg M D
Department of Obstetrics and Gynecology
County Hospital
S-721 89 Västerås
Sweden

Acta Obstet Gynecol Scand 58 321–325 1979

A COMPARISON OF THREE METHODS FOR INDUCING LABOR

Oral prostaglandin E_2 buccal desaminooxytocin intravenous oxytocin

Gert Lykkesfeldt and Mogens Osler

From the Department of Obstetrics and Gynecology Section YB Rigshospitalet University of Copenhagen Denmark

Abstract A study of labor induction in 325 patients is reported *Group 1* (77 patients with Bishop s scores 0-6) *and 2* (69 patients with Bishop s scores 7 12) were given 0 5 mg prostaglandin E_2 every half hour (maximum 5 mg per day) *Group 3* (87 patients with Bishop s scores 0-6) was given 50 International units of buccal desaminooxytocin every half hour (maximum 500 International units per day) In *Group 4* (92 patients with Bishop s scores 7 12) labor was induced by primary amniotomy and automatic oxytocin infusion by the Cardiff method

In groups 1 2 and 3 45 per cent 74 per cent and 41 per cent delivered within 48 hours while 100 per cent in group 4 delivered within 24 hours

No differences were found in either the frequency of cesarean section or the incidence of low Apgar scores

A higher but not statistically significant frequency of vacuum extraction was found in the Cardiff group (25 per cent) than in the tablet induced groups (15 per cent) There was however a significantly higher occurrence of alterations in fetal heart rate which led to instrumental intervention to hasten delivery in the Cardiff group compared to the tablet induced patients

For some years oxytocin has been commonly used for labor induction and its uterine stimulating effect when administered by either the nasal buccal or intravenous route has been well proven (1 3 4 8 9 11) An oxytocin derivate desaminooxytocin when given buccally has the same mode of action and is as effective as oxytocin (8 11)

Amniotomy followed by automatically infused i v oxytocin (Cardiff Apparatus) has been shown to be most effective (1 4) In one study 90 per cent of the women treated by this method delivered within 12 hours and by 24 hours almost all had completed delivery (1) This method however has marked disadvantages for it confines the patient to bed under intensive supervision throughout the procedure and it has also been associated with increased incidence of both vacuum extraction and cesarean section following induction using the Cardiff Stimulator (1)

Prostaglandins of the E and F series besides some other effects acts as a specific stimulant to the myometrium of the pregnant uterus Studies on the potential clinical application of these observations commenced in 1968 and since then various investigators have examined the effects of prostaglandins when administered by different routes (5 6 7 10 12)

Our study aims to compare on an open prospective basis the effectiveness of

a oral prostaglandin E_2 (Prostin[R])

b buccal desaminooxytocin (Sandopart[R])

c intravenous oxytocin (Syntocinon[R])

in inducing labor and further to study the incidence of both complications and side effects with each method

PATIENTS AND METHODS

Apart from those with diabetes mellitus all women admitted to the Obstetrical Department YB Rigshospitalet Copenhagen over a 21 month period in whom induction of labor was clinically indicated were considered eligible for recruitment into the study A total of 337 patients enrolled but 12 of them failed to adhere accurately to the study protocol and were therefore dropped from the investigation The final analysable study population consisted of 325 patients All patients had consequtive registration numbers Those with *even* numbers would if admitted for induction receive prostaglandin treatment whilst those with *odd* numbers would receive either buccal desaminooxytocin or intervenous oxytocin Allocation to the precise treatment regime was dependent on the Bishop s score on admission The treatment groups were as follows

Treatment group 1 77 patients (52 per cent primiparous) Bishop s score less than 7 Oral prostaglandin E_2

Treatment group 2 69 patients (51 per cent primiparous Bishop s score 7 or more Oral prostaglandin E

Treatment group 3 87 patients (52 per cent primiparous) Bishop s score less than 7 Buccal desaminooxytocin

In groups 1 2 and 3 amniotomy was never performed before regular contractions had been established and the cervix was dilated at least 3-4 cm

Table I *Parity and time of gestation of all 325 patients*

Treatment group	No of patients	Primi parity		Time of gestation in weeks		
		No	per cent	≤38	39–41	≥42
1	77	40	52	4 (5%)	46 (60%)	27 (35%)
2	69	35	51	1 (1%)	44 (64%)	24 (35%)
3	87	45	52	3 (3%)	54 (6[illegible]%)	30 (34%)
4	92	44	48	5 (5%)	59 (64%)	28 (30%)

Treatment group 4 92 patients (48 per cent primiparous) Bishop s score of 7 or more Low amniotomy followed by intravenous oxytocin by the Cardiff method

Parity and gestation time are shown in Table I

Patients in groups 1 2 and 3 who failed to deliver within 48 hours from commencement of therapy were regarded as primary treatment failures In these cases an individualized form of treatment was adopted and consisted of either a further course of tablets amniotomy together with oxytocin infusion or Cardiff Stimulation

The main indications for labor induction are listed in Table II

Dosage and administration

Treatment group 1 Patients were given 0.5 mg prostaglandin E_2 tablets The tablets were swallowed with a small glass of water (100 ml) The patient started with 0.5 mg and continued with 0.5 mg every half hour until a total of 5 mg had been given The treatment was discontinued however when regular contractions had been established or if there were signs of too powerful or too frequent contractions On the next day the procedure was repeated if delivery had not

group 2 Patients were given exactly the same as group 1

ent group 3 Patients were given 50 IU buccal desam oxytocin the tablets being placed between cheek and gum on the left and right side of the mouth alternatively 50 IU was given every half hour until total of 500 IU had been given Before each new administration the oral cavity was rinsed out with water in order to remove any residue from the previous tablet administration When regular labor activity had been established the dosage was reduced to 1/2 tablet every half hour If there were signs of too powerful or too frequent contractions the treatment was discontinued On the next day the procedure was repeated if delivery had not yet started

Treatment group 4 Low amniotomy preceded the intravenous administration of oxytocin using the Cardiff Apparatus (1 4) With this method the quantity of the drug infused is automatically increased until contractions of [illegible] ble strength duration and frequency have been established

STATISTICAL ANALYSIS

The Chi Squared Test with Yates correction have been used for calculating the probability value (Level of significance $p<0.05$)

RESULTS

The results of the different treatments are shown in Table III Induction of labor was regarded as successful when delivery was completed within 48 hours of commencement of treatment For the two groups of patients with low Bishop s score the success rate was 45 per cent in group 1 and 41 per cent in group 3 There was no statistical significant difference between these groups ($0.75>p>0.70$)

For the two groups of patients with a high Bishop s score group 2 showed a success rate of 74 per cent while group 4 had 100 per cent within 24 hours. The *frequency of non instrumental* and vaginal delivery in groups 1 and 2 and 3 was 74 per cent 75 per cent and 74 respectively while in group 4 it was lower 68 per cent though the difference was not significant ($0.30>p>0.25$)

Table II *Clinical indications for labor induction*

Main indication	Group 1		Group 2		Group 3		Group 4	
	No	per cent	No	per cent	No	per cent	No	per cent
Prolonged pregnancy[1]	23	30	21	30	29	33	[illegible]9	3[illegible]
Large fetus[2]	16	[illegible]1	19	28	22	25	22	[illegible]4
Pre-eclampsia	19	25	17	25	20	23	21	23
Other indications	19	25	12	17	16	18	[illegible]0	2[illegible]
No of patients	77		69		87		9[illegible]	

1) *Prolonged pregnancy* was defined as 10 days or more overdue from the estimated date of delivery
2) *Large fetus* was diagnosed when a clinical estimate of fetal weight was greater than 3 800 grams.

Table III *Results of the treatment (total number of patients = 325)*

Treatment group	No of patients	Delivery within 0 – 24 hours		Delivery within 0 – 48 hours		Patients with noninstrumental vaginal delivery)	
		No	per cent	No	per cent	No	per cent
1	77	22	29	35	45	57	74
2	69	38	55	51	74	52	75
3	87	21	24	36	41	64	74
4	92	92	100	92	100	63	68

)Prophylactic episiotomy has been included in non-instrumental vaginal deli ery

Complications and side effects A survey of the complications and side effects encountered is presented in Table IV The incidence of placental retention detached cotyledon or cervical rupture was low and without significant differences in the groups Similarly the number of babies born with an Apgar score lower than 7 after one minute was low There were 2 cases of transitory overstimulation resulting in hypertonus however in neither case was the fetal heart rate affected and following uneventful vaginal delivery both infants had normal Apgar scores

Vacuum extraction and cesarean section occurred relatively frequently in all four groups In assessing these figures it must be remembered that some patients in group 1 2 and 3 who failed to respond to the primary treatment regime were then treated on an individual basis with amniotomy oxytocin infusion etc These patients are included in the overall total listed

In order that a direct comparison can be made which accurately reflects the incidence of the more important complications attributable to the *primary* treatment a chart showing these is presented in Table V From this it will be seen that the frequency of vacuum extraction was 10 per cent higher in the Cardiff induced patients compared with the tablet induced ones This difference however did not achieve statistical significance ($0\ 10 > p > 0\ 05$) There were no differences in the frequency of cesarean section On the other hand the incidence of alterations in fetal heart rate resulting in expedition of delivery either by vacuum extraction or section was significantly higher in the Cardiff group than in the tablet induced patients ($0\ 01 > p > 0\ 005$)

Of the tablet induced patients 145 (78 per cent) were delivered vaginally without the use of instruments compared with 63 (68 per cent) of the Cardiff group The difference was not significant ($0\ 20 > p > 0\ 10$)

During the entire period of induction the fetal heart rate and the uterine contractions were monitored electronically in all patients in group 4 using a Hewlett Packard cardiotocograph Patients on tablet regimes started ambulant and were if indicated also supervised electronically by a Hewlett

Table IV *Complications and side-effects*

	Group 1	Group 2	Group 3	Group 4
Obstetrical/fetal complications				
Fetal cardiac dysrhythmia resulting in intervention to accelerate delivery	4	2	4	16
Vacuum extraction	8 (10 per cent)	11 (16 per cent)	15 (17 per cent)	23 (25 per cent)
Cesarean section	12 (16 per cent)	7 (10 per cent)	9 (10 per cent)	6 (7 per cent)
Overstimulation	0	1	0	1
Retained placenta or detached Cotyledon	2	3	4	4
Cervical rupture	0	0	1	1
Apgar score < 7 after 1 minute	5	2	3	4
Maternal side-effects				
Nausea/vomiting	6	3	0	0
No of successful inductions i e delivery within 48 hours	35 (45 per cent)	51 (74 per cent)	36 (41 per cent)	9? (100 per cent)
Total no of patients	77	69	87	9?

Table V *Comparison of some major complications*

Type of complication	Incidence in patients *exclusively* tablet induced		Incidence in Cardiff induced patients	
	No	per cent	No	per cent
Vacuum extraction	28	15	23	25
Cesarean section	15	8	6	7
Fetal cardiac dysrythmia resulting in intervention to accelerate delivery	12	6	16	17
Total No of patients	187[1]		92[2]	

[1] 80 per cent of all patients in groups 1 2 and 3
[2] group 4 as a total

Packard cardiotocograph (76 patients or 41 per cent thus supervised for various periods)

325 infants were born the perinatal mortality rate was nil Apart from one child born with the Pierre Robin syndrome and another with esophageal atresia all the children were found to be healthy and displayed no abnormalities on discharge

DISCUSSION

It is well established that amniotomy as such is potent in provoking contractions (3) The effect of such a procedure is demonstrated by comparing the success rates of groups 2 and 4 In both these groups the Bishop s score was at least 7 yet in group 4 where amniotomy was performed the success rate was increased In groups 1 and 3 where the Bishop s score was less than 7 it will be seen that oral prostaglandin E and buccal desaminooxytocin in the dosages employed were equally effective in initiating labor

The result of the present investigation demonstrate moreover that the effect of oral prostaglandin E is considerably greater at a high Bishop s score than at a lower one a factor which is well known for oxytocin and desaminooxytocin (1 2 8 9 11) When the results of induction using oral prostaglandin E (groups 1 and 2) are compared with other investigations (5 6 7 10 12) it will be noted that our success rates of 45 per cent in patients with a low score and 74 per cent in those with a high score are low In some studies however *primary* amniotomy was performed while in others the relationship to *primary* amniotomy is not clear These circumstances together with considerable differences in the mode of reporting make it difficult to arrive at accurate comparisons of the results of these investigations

The frequency of vacuum extraction in the Cardiff induced patients was 25 per cent which is somewhat higher than the figure of 15 per cent for the patients induced with tablets (Table V) However this difference is not significant (0 10 > p > 0 05) On the other hand the incidence of alterations in fetal heart rate resulting in instrumental delivery by vacuum extraction or section was significantly higher in the Cardiff group compared with the tablet induced patients (0 01 > p > 0 005) (Table V) This finding could indicate that induction with the Cardiff Apparatus is potentially more stressful and carries a greater risk of fetal asphyxia during delivery than induction with tablets Other factors however may also have played a part During the course of treatment all patients in group 4 (the Cardiff group) were under continuous electronic supervision compared with only 41 per cent in groups 1 2 and 3 (tablet groups) The difference in the use of intensive monitoring may have contributed to the higher incidence of intervention carried out on suspicion of fetal asphyxia in group 4 The Apgar scores moreover show no difference after 1 minute between the groups which suggests that in fact the children in group 4 had not been exposed to asphyxia more frequently than those in the other groups

It can be concluded that oral prostaglandin E and desaminooxytocin used in the regimes described are equally effective in inducing labor Minor gastrointestinal side effects can occur in patients receiving the prostaglandin

The Cardiff system has been shown to be effective in inducing labor and all patients in whom this method was employed delivered within 24 hours of the start of treatment The results of our study however suggests that this method may involve a greater risk of the delivery being terminated by vacuum extraction of cesarean section following the detection of alterations in the fetal heart rate This finding warrants

further investigation using a larger patient population in order to establish whether such disturbances are in fact caused by transitory intrauterine fetal distress or are the result of the intensive monitoring allowing accurate and rapid observation of momentary fluctuations in fetal heart rate during delivery. The Cardiff system does not solve the problem that exist in patients with a low Bishop s score for one of the prerequisites before initiation of this system is sufficient cervical dilatation to enable amniotomy to be performed and an intrauterine catheter to be inserted.

As the complications of any method for labor induction available today are not negligible such a course of action should only be undertaken when there is a genuine clinical indication and not merely for the sake of convenience.

ACKNOWLEDGEMENTS

We should like to thank Messrs Upjohn S A for the supply of prostaglandin E_2 tablets (Prostin[R])

REFERENCES

1 Bangstrup L Jessen P & Osler M Igangsættelse af fødsler med et automatisk oksytocin infusionssystem Ugeskr Læg *137* 1095 1975
2 Bishop E H Pelvi scoring for elective induction Obstet Gynecol *24* 266 1964
3 Bradford W P & Gordin G Induction of labour by amniotomy and simultaneous syntocinon infusion J Obstet Gynaec Brit Cwlth *75* 698 1968
4 Francis J G Turnbull A C & Thomas F F Automatic oxytocin infusion equipment for induction of labour J Obstet Gynaec Brit Cwlth *77* 594 1970
5 Friedman E A & Sachtleben Marlene R Oral prostaglandin E_2 for induction of labor at term Obstet Gynecol *43* 178 1973
6 Gabert H A Brinton J & Brown B Induction of labor with oral prostaglandin E_2 Obstet Gynecol *126* 333 1976
7 Lauersen N H & Wilson Kathleen H Induction of labor with oral prostaglandin E_2 Obstet Gynecol *44* 793 1974
8 Lykkesfeldt G Veinduction med bukkalt oksytocin og demoksytocin Ugeskr læg *138* 1704 1976
9 Möller K & Osler M Induction of labour A comparison of intravenous intranasal and transbuccal oxytocin Acta Obstet Gynecol Scand Suppl *9* 59 1967
10 Nilson G H & Bryans C I A comparison of oral prostaglandin E_2 and intravenous oxytocin for induction of labor in normal and high risk pregnancies Am J Obstet Gynecol *1'6* 549 1976
11 Poulsen E F The induction and stimulation of labour with buccal desaminooxytocin and oxytocin tablets Acta Obstet Gynecol Scand *52* 303 1973
12 Tsakok F H M Grudzinskas J G Karim S M M & Ratnam S S The routine use of oral prostaglandin E_2 in induction of labour Brit J Obstet Gynaec *82* 894 1975

Submitted for publication March 14 1978

Gert Lykkesfeldt M D
Department of Obstetrics and Gynecology
Section YB
Rigshospitalet
University of Copenhagen
Copenhag n
Denmark

Table V *Comparison of some major complications*

Type of complication	Incidence in patients *exclusively* tablet induced No	per cent	Incidence in Cardiff induced patients No	per cent
Vacuum extraction	28	15	23	25
Cesarean section	15	8	6	7
Fetal cardiac dysrythmia resulting in intervention to accelerate delivery	12	6	16	17
Total No of patients	187[1]		92[2]	

[1] 80 per cent of all patients in groups 1 2 and 3
[2] group 4 as a total

Packard cardiotocograph (76 patients or 41 per cent thus supervised for various periods)

325 infants were born the perinatal mortality rate was nil Apart from one child born with the Pierre Robin syndrome and another with esophageal atresia all the children were found to be healthy and displayed no abnormalities on discharge

DISCUSSION

It is well established that amniotomy as such is potent in provoking contractions (3) The effect of such a procedure is demonstrated by comparing the success rates of groups 2 and 4 In both these groups the shop s score was at least 7 yet in group 4 where otomy was performed the success rate was increased In groups 1 and 3 where the shop s score was less than 7 it will be seen that oral prostaglandin E_2 and buccal desaminooxytocin in the dosages employed were equally effective in initiating labor

The result of the present investigation demonstrate moreover that the effect of oral prostaglandin E_2 is considerably greater at a high Bishop s score than at a lower one a factor which is well known for oxytocin and desaminooxytocin (1 2 8 9 11) When the results of induction using oral prostaglandin E_2 (groups 1 and 2) are compared with other investigations (5 6 7 10 12) it will be noted that our success rates of 45 per cent in patients with a low score and 74 per cent in those with a high score are low In some studies however *primary* amniotomy was performed while in others the relationship to *primary* amniotomy is not clear These circumstances together with considerable differences in the mode of reporting make it difficult to arrive at accurate comparisons of the results of these investigations

The frequency of vacuum extraction in the Cardiff induced patients was 25 per cent which is somewhat higher than the figure of 15 per cent for the patients induced with tablets (Table V) However this difference is not significant ($0\ 10 > p > 0\ 05$) On the other hand the incidence of alterations in fetal heart rate resulting in instrumental delivery by vacuum extraction or section was significantly higher in the Cardiff group compared with the tablet induced patients ($0\ 01 > p > 0\ 005$) (Table V) This finding could indicate that induction with the Cardiff Apparatus is potentially more stressful and carries a greater risk of fetal asphyxia during delivery than induction with tablets Other factors however may also have played a part During the course of treatment all patients in group 4 (the Cardiff group) were under continuous electronic supervision compared with only 41 per cent in groups 1 2 and 3 (tablet groups) The difference in the use of intensive monitoring may have contributed to the higher incidence of interventions carried out on suspicion of fetal asphyxia in group 4 The Apgar scores moreover show no difference after 1 minute between the groups which suggests that in fact the children in group 4 had not been exposed to asphyxia more frequently than those in the other groups

It can be concluded that oral prostaglandin E_2 and desaminooxytocin used in the regimes described are equally effective in inducing labor Minor gastro-intestinal side effects can occur in patients receiving the prostaglandin

The Cardiff system has been shown to be effective in inducing labor and all patients in whom this method was employed delivered within 24 hours of the start of treatment The results of our study however suggests that this method may involve a greater risk of the delivery being terminated by vacuum extraction of cesarean section following the detection of alterations in the fetal heart rate This finding warrants

Acta Obstet Gynecol Scand 58 327–334 1979

THE PROTRUSIONS FROM THE CERVICAL CANAL AT THE SCAR OF A PREVIOUS CESAREAN SECTION

P J H van Vugt

From the Department of Obstetrcis St Jozef Ziekenhuis Gouda Holland

Abstract By comparing the condition of the cervix at the time of a cesarean section with the findings at subsequent hysterography in 68 patients it is considered likely that the thickness of the scar depends primarily on the thickness of the lower uterine segment at the time of the section and on the site of the incision The prognostic significance of these findings is discussed on the basis of a theoretical approach to the development at or near the scar of previous cesarean section

Hysterography is generally agreed to be a useful method for determining the quality of the scar in the uterus after a cesarean section a deep protrusion signifies poor a small or absent protrusion signifies good healing The X ray pictures are used as a guide to the method of future delivery Our initial observations showed that even after a satisfactory postoperative course deep protrusions can be found This initiated the idea that deep protrusions are not always the result of poor healing For this reason we collected data on cesarean scars from 68 patients

MATERIAL AND METHODS

The incision in the uterus in our 68 patients was invariably a low transverse one closed in two layers *interrupted stitches* of No 2 catgut carefully avoiding the endometrium The stitches were passed through the muscular wall at about ½ cm from the edge of the wound

Table I *The age of the patient and the inner contour of the cervix*

Age (years)	Protrusion large	small	none	total
≤19	—	2	—	2
20–24	2	8	2	12
25–29	8	13	5	26
30–34	3	5	6	14
35–39	4	2	4	10
≥40	—	3	1	4
Total	17	33	18	68

The quality of the scar in these patients was determined in two ways by hysterography and by palpation

1 Hysterography This examination was carried out with 40 per cent lipiodol some three months after the operation Anterior lateral and diagonal views were taken The tip of the instrument introduced into the cervix was kept as short as possible to achieve optimal filling of a distal scar Contrast media of lower viscosity passed the cervix and the uterus too rapidly and so fails to reveal defects of the cervical wall at the scar

The hysterographically demonstrated protrusions were divided into large and small ones depending on their depth i e greater or smaller than 4 mm This limit was easily determined because this was the diameter of the end of the instrument introduced into the cervix

2 Palpation of the scar The intracervical scar was routinely palpated following a subsequent vaginal birth or a repeat cesarean section to discover possible dehiscense and to judge its quality and thickness compared to the surrounding tissues

Statistics The Chi square test was used to test the significance of the results

RESULTS

1 Hysterography was performed on 68 consecutive cesarean patients Of these 18 were found to have no protrusions *33 a small and 17 a large protrusion* These data were related to

a) the age of the patient at the time of operation

b) the number of births prior to the time of the operation

c) the postoperative course

Table II *Parity and the inner contour of the cervix*

Parity at the time of C S	Protrusion large	small	none	total
0	10	19	6	35
I and II	5	12	5	22
III and more	2	2	7	11
Total	17	33	18	68



Fig 3 Hysterogram three months after a cesarean section with a transverse incision in the thin lower uterine segment on which occasion an old scar was excised a) front view b) lateral view



Fig 4 Hysterogram three months after normal labor following two previous elective sections

CASE REPORTS

a The first is a case of a ruptured uterus after a previous cesarean section not however in the scar of that operation but adjacent to the scar of a previous corporeal rupture Uterine rupture occurred at the very beginning of labor the fetus was expelled into the abdominal cavity At laparotomy it was clear that the originated from the region *next to the scar* of corporeal rupture which had been treated This was confirmed by histological inves tion At the other side of the old thick scar the uterine wall was extremely thin with bleeding and tearing of the tissue (fig 2)

b This patient showed a deep protrusion on the hysterogram (fig 3) so the wall was *thinner* in that region Evenso after a subsequent labor the scar could be felt as a slight elevation in the lower uterine segment

c The scar of a former cesarean section could be felt at an elective repeat section it was *as thick as* the rest of the lower uterine segment Subsequent hysterography showed two small protrusions

d After two elective sections this patient gave birth spontaneously A scar could be felt as a slightly elevated ridge After three months the hysterogram showed a small protrusion (fig 4) showing that the scar was *thinner* than the surrounding cervical tissue

e The first section in this patient was done because of malposition after dilatation was complete The second section was done after some hours of labor the *thinness* of the lower uterine segment was striking The hysterogram showed two deep protrusions (fig 5)

f This patient also had two sections both at full dilatation At the second section the first scar was felt to be *level* with the rest of the lower uterine segment but the hysterogram showed two deep protrusions (fig 6)

DISCUSSION

1 The origin of the hysterographic pictures We found deep protrusions particularly after excessive stretching of the lower segment of the uterus whilst after elective sections deep protrusions were rare In our cases the prevalence of elective section increased with the age of the patient and less obviously with parity This observation may be closely related to the primary pathology e g arrest of labor in the younger nulliparous women and the rarity of fetal distress as a reason for section in the older multiparous women

Placenta previa and severe fetal distress were evenly divided over the age and parity groups

We do not consider it likely that increasing age or multiparity respectively are responsible for the differences in hysterographic views It is more likely that the condition of the lower segment a few months after the cesarean section depends on *the thickness of the lower segment at the time of the operation* If at cesarean section the uterine wall at the site of incision is thick there tends to be no or only a small protrusion while if the wall is thin the protrusion is often large

The lower segment of the uterus is usually thicker at elective section than when the women has been in

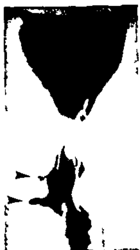


Fig 5 Hysterogram after two sections both performed during labor



Fig 6 Hysterogram after two sections both performed during labor

labor some time generally speaking the more advanced the labor the thinner the wall will be We feel that this also explains why as some investigators have reported the picture after repeated section which tend to be elective procedures is similar to that found after the first section We have the same experience but the examples given above under *e* and *f* demonstrate that this is not always the case after a second operation performed after trial of labor

It seems doubtful if the site of incision per se has any influence other than being associated with a different thickness of the uterine wall

Other factors than the thickness of the wall may contribute to the hysterographic findings e g

suturing the endometrium into the wound

infection of the wound

necrosis in the wound

partial filling of the defect with mucus at the time of the later radiography

The retraction and subsequent involution are shown diagramatically using our method of closing the uterus (fig 7)

2 The prognostic significance of the hysterographic pictures The likelihood of a rupture of the scar during a subsequent pregnancy or labor depends entirely on the remaining thickness of the uterine wall What forces are working on each side of the scar? Rupture of the wall of a hollow organ depends on the stretching forces in the wall and on the resistance the wall can offer The total strength of each cross section of the wall has to be equal (Hook s law) Each fiber in the wall has its share in the resistance to this parietal stretching The total resistance that can be offered therefore depends on the number the thickness and the density of the fibers in that section The wall will distend evenly only if each cross section contains the same quantity and quality of fibers If one area can not offer as much resistance as the rest of the wall that area will stretch more and eventually rupture

Because scar tissue usually contains a solid network of numerous collagenous fibers with considerable tensile strength and less elasticity as compared with the surrounding normal wall a stretching force will stretch the scar less than the normal wall The broader the scar the more fibers and the less force is exerted on each So some preceding thinning of the scar in the wall may not lead to a weak spot But if there are only a few fibers left (deep protrusion small scar) those fibers have to stand the whole exerted force and will reach their stretching limit soon after which rupture will take place So a thinned out scar is more liable to rupture but an uterus containing a sound scar of even width can also rupture

To understand where such a piece of tissue (fig 8a) will eventually burst we have to realize that in the transitional region between the scar tissue and the normal tissue the fibers do not run straight but in a curve when under tension (fig 8b) Because the total strength to resist the stretching force per cross section is equal (Hook s law) the parietal tension S in the wider part is relatively small which is apparent from the following equation

$$S \times R \times \delta = S \times R \times \delta$$

(S S and S are the pulling powers in the different cross sections R R R the thic

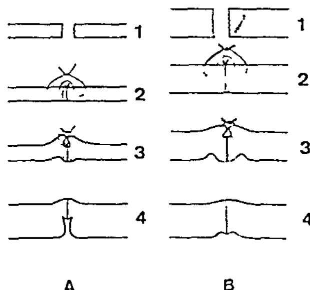


Fig 7 Diagram of the suturing of the wound in a stretched out lower uterine segment (A) and of a thick lower uterine segment (B) followed by retraction and involution
1 situation before suturing 2 situation after completing the first row of sutures while placing the second row 3 situation after completing the second row of sutures 4 situation after retraction and involution

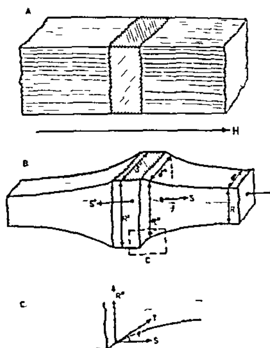


Fig 8 Diagram of the results of traction in a fragment of tissue in which there is a thick inelastic scar

that sections δ δ δ the width of the tissue at that sections) Because there are more collagenous fibers and because the force S is relatively small of elastic deformation will be reached slower In this connection it is not of great importance t the fibers may run in every direction for the stretching takes place in a certain direction anyway Examining however the junction between the scar and the normal tissue we note that the thickness (R δ") closest to the scar is even greater than that of the remaining piece of tissue but the potential parietal tension is less than S (fig 8b)

$$S \times R \times \delta = S \times R \times \delta$$

This parietal tension however has to be absorbed by the stretching of the available fibers in a different direction The tension in these fibers in a state of equilibrium can be called T and is greater than S

$$T = \frac{S}{\cos \varphi}$$

in which φ is the angle of the fibers to the original direction When stretching is going on φ increases so T increases also and the limit of elasticity is reached the sooner next to the scar Obviously this is true only for thick scars (fig 8c)

Because the lower segment of the uterus becomes thinner during labor it applies mainly to scars following the incision of a thick lower uterine segment Rupture not in but next to a corporeal scar may occur if the uterus is unduely distended A predisposition to such a rupture exists also after degeneration of elastic fibers in that area or if the uterine wall has been weakened by other causes such as abnormally wide bloodvessels or the ingrowth of endometrium at the site of the stitches Time may be important with scar rupture during a short period of stress some fibers may rupture but complete rupture does not occur if the stretching force is removed in time When a new stretching force (new pregnancy) is applied rupture may be the more likely In individual cases we do not know whether a weak scar is present or not In fig 9 we have sketched diagrams of alternative patterns or impending uterine rupture based on this hypothesis and our clinical observations

CONCLUSIONS

The picture of the internal contour of the cervix some months after a cesarean section provides an indication of the thickness of the uterine wall in the region

	Situation before the pregnancy	Situation later in pregnancy	Situation during labor	Situation in over stretching	Situation at the moment of rupture
Well healed elastic scar after primary cesarean section					
Well healed elastic scar after secun dary cesarean section					
Broad not elastic scar after primary cesarean section					
Broad not elastic scar after secun dary cesarean section					
Thin scar					
Dehiscence of the scar					

Fig 9 Diagram of the development of rupture in or near a variety of scars resulting from cesarean section

of the scar It seems likely that this depends primarily on the thickness of the uterine wall at the site of the incision and need not be a sign of poor healing in the scar

A fairly thick scar (either none or a small protrusion) is not a guarantee against rupture nor need a small scar (deep protrusion) give rise to rupture Most liable to rupture are broad thin scars (deep and wide protrusion)

ACKNOWLEDGEMENT

We wish to thank Dr Th Z J v d Net for his kind assistance with the statistical analysis

Submitted for publication October 14 1977

P J H van Vugt
Groenstraat 78
Udenhout
Holland

Acta Obstet Gynecol Scand 58 335–342 1979

EFFECTS ON FETAL BREATHING MOVEMENTS OF MATERNAL CHALLENGES

Cross over study on dynamic work static work passive movements hyperventilation and hyperoxygenation

Karel Maršál Gerhard Gennser and Olof Löfgren

From the Department of Obstetrics and Gynecology University of Lund Allmänna Sjukhuset Malmö Sweden

Abstract Ten women in the last trimester of a normal pregnancy were subjected to five different loads in a cross-over study Fetal breathing movements (FBM) fetal heart rate (FHR) maternal heart rate (MHR) and mean arterial pressure (MAP) maternal transcutaneously measured pO_2 (Tc pO_2) and the energy supply to the Tc pO_2 electrode were recorded continuously before during and after the load Maternal capillary pH and pCO_2 were measured at three representative time points The immediate responses of the incidence of FBM to the different challenges were increase after dynamic work (bicycle test) no change after static work (isometric muscle contraction) and passive movements decrease after hyperventilation and hyperoxygenation FHR was unaffected by all challenges The FBM incidence varied in parallel with pCO_2 after dynamic work and hyperventilation and inversely with the Tc pO_2 rise caused by hyperoxygenation Maternal pH was increased after passive movements (no change in FBM) and after hyperventilation (decreased incidence of FBM) FBM seem to be more sensitive to environmental changes than is the FHR Mechanical stimuli to the uterus were not responsible for the augmentation of FBM seen after the bicycle test The present observations reveal the multifactorial nature of the regulation of FBM and support the role of CO_2 as a major stimulator of breathing movements also in prenatal life

The impact on the human fetus of maternal physical activity has been little investigated in recent years This apparent lack of attention is remarkable in view of the common use of bed rest as treatment for complications of pregnancy Among available data the fetal heart rate has been found to be largely unchanged by submaximum maternal exercise (14 32) Recently (26) it was demonstrated that a work load of short duration applied to women in the last trimester of normal pregnancies led to a transient marked increase in the fetal breathing movements (FBM) This effect appeared in the absence of changes of the basal heart rate of the fetus (26) The normal regulation of FBM in man is at present unknown as are the mechanisms by which the FBM are affected by maternal work In an attempt to further elucidate the cause-effect relation between FBM and maternal exercise a study was performed in which pregnant women were subjected to five different challenges The influence of these challenges on various facets of the physiological state of the women were compared with the effects on the FBM

MATERIAL AND METHODS

Ten pregnant women in the last ten weeks of gestation took part in the study after giving their informed consent Their ages ranged 21 33 (median 27 3) years six of them were primigravidae Apart from one woman who had slight cholestasis all had a normal pregnancy and were subsequently delivered vaginally In two a low vacuum extraction was performed because of imminent fetal distress One newborn infant had an Apgar score of 6 at one min and 9 at five min the others had initial Apgar scores of 7 or more All the infants were born after 36 weeks of pregnancy One was small for the gestational age according to the Swedish standards (37) weighing 2 140 g at birth in the 39th gestational week A retrospective review of this latter case did not reveal any significant difference in other parameters when compared with the remaining nine cases The test period which on average lasted 4 weeks occurred during the last 10 weeks of gestation

All tests were performed between 8 a m and noon with the women in semi recumbent position The study was scheduled to subject every woman to the five following tests

1 Dynamic work
2 Passive movements
3 Sustained voluntary isometric muscle contraction
4 Hyperventilation
5 Hyperoxygenation

The order of tests was randomized in accordance with a cross-over type of study Two to seven days were allowed to elapse between consecutive tests Three of the women started labor after three challenges leaving seven women in the full cross-over study

The schedule of each test was as follows After a 30 min control period the test load was given during 5 min followed by another 30 min observation time

1 *Dynamic work* was performed on a bed type bicycle ergometer The magnitude of the work load was 80 W

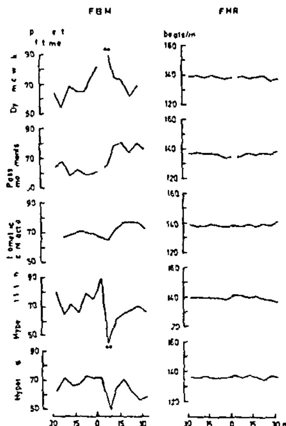


Fig. 1. Response of fetal breathing movements (FBM) and fetal heart rate (FHR) to five different challenges in 10 pregnant women. Curves drawn between means of 5 min periods. Shaded areas denote the 5 min duration of challenge. Significance of difference to entire control period (this and following Figures): * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

Calibration of the ergometer was achieved by measuring the oxygen uptake at steady state in two male volunteers when pedalling on three different occasions (mean oxygen uptake = 1 420 ml/min).

2. In the *passive movement* test, the women's feet were put on the bicycle ergometer pedals, which were then rotated by the operator at the same speed as used in the dynamic work test.
3. A voluntary *isometric muscle contraction* was achieved by sustained hand grip with a power chosen to a third of the maximum power accomplished by the particular woman.
4. During *hyperventilation* the woman was breathing room air at maximum speed and depth.
5. *Hyperoxygenation*. During this test the women breathed oxygenenriched air. The percentage of oxygen added was regulated to keep the transcutaneously measured pO_2 (see below) level at 70-100 per cent above the level found during the control period.

The following parameters were registered during the tests: *Fetal breathing movements* (FBM) were measured continuously by an ultrasonic A mode echoscope (Ekoline 20[R], Smith Kline Instr. Inc., Palo Alto, Calif.) according to the method described by Boddy and Robinson (2) and a pen recording of the signals was made (Polygraph Model 7 B, Grass Instrument, Quincy, Mass.). During the periods of dynamic work and passive movements the recording of FBM could not be used because of the spurious signals caused by the maternal movements. The records were evaluated manually according to Parmelee *et al* (31). The entire record was divided into 20-sec periods and the FBM for each period were classified in one of four patterns: regular, irregular, periodic and apneic. The percentage of time during which each FBM pattern was present was then calculated for every 5 min period. To obtain perspicuity this report gives only the percentage of time that there was irregular breathing, but this correlates closely with the total incidence of FBM (25). One of the authors (K. M.) analysed all records. To avoid bias during the evaluation all FBM records were cut into 5 min pieces, coded and read blind. The results were obtained after reconstruction of the records.

Fetal heart rate (FHR) was counted visually every second min on the echoscope screen where the fetal heart echo was displayed throughout the test. The fetal heart movements could not be recorded during the periods of dynamic work test and passive movements test for the same reasons as given for FBM.

The *maternal breathing rate* (MB) was calculated from signals from a thermistor applied to one nostril.

The *maternal heart rate* (MHR) was obtained from electrocardiogram recorded by conventional chest electrodes.

The *maternal brachial blood pressure* was measured at 4 min intervals by an automatic instrument (type 15100 A, Godart NV, Utrecht). The results are presented as the mean arterial pressure (MAP) calculated according to the formula (5): ⅓ (systolic BP + 2 diastolic BP).

Maternal transcutaneous pO_2 (Tc pO) was measured by a Radiometer TCM 1 unit. The Tc pO_2 electrode used was a Clark type electrode modified according to Huch (15). The Tc pO (mm Hg) and the electric energy supply (mW) necessary to keep the heat element of the electrode at 44.5 C were continuously recorded on a polygraph (Linear Corder Mark III, Watanabe Instr. Corp., Tokyo). The electrode was attached to the skin in the subclavicular area. The means of the Tc pO_2 and the relative levels of energy supply were calculated from the records for every 5 min period. The correlation between the pO_2 values measured in arterial blood samples and by transcutaneous measurements is strong ($r = 0.95$, $p<0.001$); the mean difference between values obtained by these two methods is 16.5 mm Hg (unpublished). Thus the absolute values of Tc pO differ from those of pO_2 in systemic blood, but the changes of the Tc pO_2 levels are representative for changes of the state of oxygenation.

Statistic evaluations of results were done by Student's t test for paired observations and by variance analysis.

RESULTS

The data obtained at the five different interventions are given in Figs 1-3 and Tabels I and II which include all 10 women.

The validity of the cross over study concerning the effect on FBM was tested on the seven women sub-

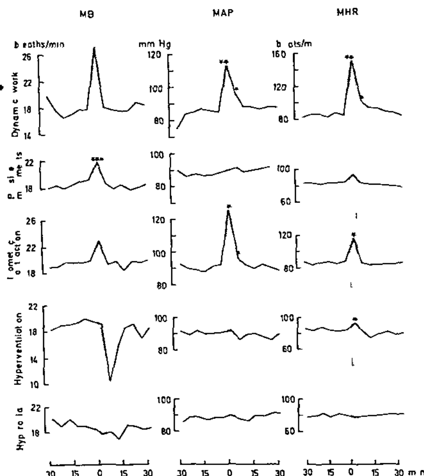


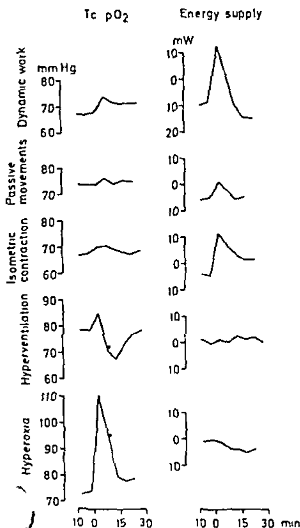
Fig 2 Effects of five challenges on breathing rate (MB) mean arterial pressure (MAP) and heart rate (MHR) of 10 pregnant women For details see Fig 1

jected to all five challenges An analysis of variance with a randomized block design was used (Table III) The statistical evaluation showed that the subject groups were very homogenous in their reactions and that the various loads had highly different effects in dicating that the cross-over test had good discrimina tion

Dynamic work Immediately after the end of this stress a pronounced increase in the incidence of FBM occurred with virtual abolition of the apneic periods As pointed out in Methods the fetal parameters could not be followed during the periods of maternal movements A rise of FBM was evident already at the onset of the cycling test but did not reach the level seen in the recovery phase The FHR remained un changed by this test and also by all the other four tests

The maternal circulation responded by an increase in blood pressure which primarily affected the systolic pressure and by doubling the heart rate Also the maternal breathing rate increased sharply during the cycling and returned with the blood pressure and heart rate to control levels within 10 min after the end of exercise The Tc pO_2 rose from 68 mm Hg to a maximum of 75 mm Hg at 5 min after the work en ded The energy supply to the O_2-electrode reached a peak during the exercise and was swiftly returning to control level in the recovery phase At 5 min after the end of the exercise the maternal capillary pCO_2 showed a significant though small increase (from 33 8 to 35 6 mm Hg) and maternal pH was unchanged

Passive movements After the end of this challenge the FBM incidence was at control level however 10 min later a rise had occurred which persisted through out the observation time The FHR was not affected nor was the maternal blood pressure A slight in crease in both maternal pulse and breathing rate subsided immediately after the exercise No change oc



3. Effects of five challenges on maternal transcutaneous pO_2 (Tc pO) and relative energy supply to the electrode Details see Fig 1

curred in Tc pO_2 whereas a small transient increase in energy supply was observed The maternal blood pH had increased somewhat after the exercise the pCO_2 being unchanged

Isometric contraction This challenge did not cause any alteration of the two fetal parameters whereas an increase of short duration was noted in the rates of maternal breathing and pulse Also the blood pressure rose and this was observed for both the systolic and the diastolic pressure The Tc pO_2 did not change but the energy supply increased and subsided slowly after the test No alteration in the capillary pH and pCO_2 was noted

Hyperventilation During hyperventilation a slight increase in FBM was seen followed by a decrease below the control level after the test ended The FHR was not affected and maternal blood pressure and pulse were unchanged During hyperventilation a slight rise of Tc pO_2 occurred This was followed by a fall to below the initial level coincident with the maternal bradypnoea after the hyperventilation ceased In the early recovery phase the pCO fell from 33 0 to 28 1 mm Hg with a concomitant increase in pH from 7 45 to 7 52

Hyperoxygenation did not change the FBM during the test but caused a short decrease in their incidence in the early recovery phase FHR maternal breathing blood pressure and heart rate remained unchanged The Tc pO_2 rose markedly during the test leaving the level of the energy supply unchanged Hyperoxygenation caused no alterations in either the capillary pH or pCO_2

DISCUSSION

After the introduction of ultrasound for non invasive measurement of FBM in man (2) a succession of reports followed describing the human FBM in various situations Thus the incidence of FBM is reportedly influenced by a diurnal rhythmicity (3) the maternal blood glucose level (13) and the mode of fetal presentation (27) The effects of several drugs administered to pregnant women have also been studied (4) However at present considerable gaps exist in the knowledge of the regulation of human FBM

The pregnant women in our study were subjected to the defined challenges in order to elucidate the mechanisms responsible for in particular the exercise induced effect on the FBM The five stresses used induce several changes in the maternal state this renders it difficult to interpret the interaction with FBM but they are similar to stresses in every-day life and in obstetric practice Moreover the battery of tests in the cross-over study was designed to yield a varied response of FBM in fact the statistical analysis showed the five challenges to be highly discriminatory in respect to changes in the incidence of FBM The increased incidence of FBM recorded shortly after maternal dynamic work confirms our preliminary observations (26) The finding that after exercise the change of FBM was not associated with a change in the baseline FHR agrees with the dissociated response of these fetal parameters in chronic distress (4) or after maternal smoking (12) The present observations therefore corroborate the suggestion (4) that in cer

Table I *Maternal capillary pH in five different tests Maternal challenges were applied during the interval 0–5 min*

	Dynamic work (n = 8)			Passive movements (n = 7)			Isometric contraction (n = 10)			Hyperventilation (n = 9)			Hyperoxia (n = 9)		
Min from start	−10	5	20	−10	5	20	−10	5	20	−10	5	20	−10	5	20
Mean	7 44	7 42	7 44	7 44	7 46	7 45	7 43	7 45	7 44	7 45	7 52	7 46	7 44	7 45	7 45
±SEM	±0 01	±0 01	±0 01	±0 01	±0 01	±0 01	±0 01	±0 01	±0 01	±0 01	±0 01	±0 01	±0 01	±0 01	±0 01
Significance of difference															
t		1 838	0 429		3 545	1 225		2 182	1 037		9 390	1 134		1 577	0 857
p		>0 05	>0 05		<0 05	>0 05		>0 05	>0 05		<0 001	>0 05		>0 05	>0 05

tain situations the FBM are a more sensitive indicator of the fetal state than is the baseline FHR

The maternal *exercise on bicycle* was followed by a transient marked increase in the FBM incidence The pre exercise increase of FBM during the control period was presumably caused by the apprehension in anticipation of the test This is supported by the observation of a similar rise in the energy supply to the Tc pO_2 electrode as evidence of a maternal circulatory change just before the dynamic work In this context it is of interest that catecholamines which might be released during strain have been reported to stimulate FBM (4)

The dynamic work caused two types of changes in the maternal state First a substantial rise in the heart rate and in the mean arterial pressure These changes probably signal an augmented cardiac output as in man the increase of cardiac output in response to work is mainly effected in an elevated heart rate (35) The present data do not solve the question of whether the increased metabolic demand in the contracting leg muscles diverts blood flow from the uterus The study on pregnant women by Morris *et al* (29) that measured the clearance time of locally injected ^{24}Na showed a decrease in total uterine blood flow during exercise followed by an increase after the work load ended But these results could not distinguish between the blood flow to the placenta and that to the myometrium To the best of the authors knowledge no work has been presented to elucidate the partition of uterine blood flow in pregnant women during work But a recent study demonstrated in pregnant ewes that after exercise a redistribution of uterine blood flow occurred in favor of the placenta (7)

The second change of the maternal physiological state was indicated by the small but significant increase in maternal capillary pCO_2 after exercise This change agrees with collected data from the literature showing that mild and moderate exercise on average raises the arterial pCO_2 by 2 3 mm Hg (11) The repeatedly reported positive relationship between maternal and fetal pCO (16) suggests that a change towards maternal hypercapnia during work is also reflected in the fetus In this context the observation in Rhesus monkeys that even small elevations of fetal pCO_2 in the range of 2-4 mm Hg increased FBM (28)

Table II *Maternal capillary pCO (mm Hg) in five different tests Maternal challenges were applied during the interval 0–5 min*

	Dynamic work (n = 8)			Passive movements (n = 7)			Isometric contraction (n = 10)			Hyperventilation (n = 9)			Hyperoxia (n = 9)		
Min from start	−10	5	20	−10	5	20	−10	5	0	−10	5	20	−10	5	20
Mean	33 8	35 6	32 4	33 6	34 4	34 0	34 0	34.2	34 2	33 0	28 1	32 4	33 3	34 1	34 0
±SEM	±0 5	±0 7	±0 9	±0 9	±1 4	±1 1	±0 6	±0 8	±0 8	±0 8	±0 9	±0 8	±0 6	±0 7	±1 0
Significance of difference															
t		2 813	1 457		1 216	0 430		0 452	0 327		4 927	1 170		1 369	0 851
p		<0 05	>0 05		>0 05	>0 05		>0 05	>0 05		<0 01	>0 05		>0 05	>0 05

Table III *Variation in FBM responses between five loads and seven women in the cross over study The evaluation is based on the intraindividual differencies in the FBM incidence between the control period (−30−0 min) and the 5 min period immediately after the load*

	Subjects n=7	Challenges n=5
Variance ratio	0 998	8 0?8
Significance	$p>0\ 05$	$p<0\ 001$

is highly pertinent

In lamb fetuses electrical stimulation of the afferent sciatic nerve and also mechanical stimuli applied to the skin elicited breathing movements (36) In the present study *passive leg movements* were not immediately accompanied by a change in FBM This suggests that the bouncing of the uterus against contracting hip flexors was not a strong enough stimulus to initiate FBM and that pure mechanical stimuli were not responsible for the enhancement of FBM seen at the dynamic work test The secondary rise of FBM noted 10 min after the end of this test cannot be related to any contemporary change in maternal home

s

challenge with *isometric muscle contraction* ut any sensory stimulation to the fetus did not e any increase in FBM A similar test in men aised their heart rate and markedly elevated their blood pressure (22) The latter effect was due to a combination of increased cardiac output and peripheral vasoconstriction Our observations indicate that pregnant women react similarly to this challenge The *rise in energy supply to the Tc pO_2 electrode* does not contradict the earlier finding that cutaneous blood flow is unaltered or reduced by static work (22) The heated electrode causes a maximum dilatation of the vascular territory and the increase of the amount of energy supply therefore probably reflects the increased cardiac output The interesting question of the reaction of the uterine blood flow to local static work must remain unsolved for lack of valid data A finding of pertinence to the FBM regulation is the unchanged level of capillary pCO_2 (taken from the contralateral hand) after the end of the isometric contraction The lack of change in the pCO_2 level despite the pronounced circulatory change is probably due to the small muscle mass involved in the local work The observations in the isometric contraction test are therefore not discordant with the idea that increased CO_2 tension is a principal stimulator of FBM after maternal dynamic work

The reduction of FBM immediately after maternal *hyperventilation* concomitant with a lowering of maternal pCO_2 agrees with recent observations in women (24) and baboons (17) The present work gives no sign of influence by hyperventilation on the maternal systematic blood circulation and the data of energy supply to the Tc pO_2 electrode suggest an unchanged *skin circulation* On the other hand hyperventilation, as expected caused a moderate decrease of maternal pCO_2 and a rise of pH Hyperventilation has the merit of being a common phenomenon during pregnancy and parturition but the simultaneous change of both O_2 and CO_2 tensions complicates the interpretation relating to the effect on FBM There has been some controversy about the influence on the fetus of maternal hyperventilation Wulf (38) found a decrease in fetal pO_2 following maternal hyperventilation This was not confirmed when measuring oxygen saturation in umbilical blood (6) or fetal pO_2 in scalp blood (23) The effects of maternal hyperventilation on the fetus have long been thought to be mediated by a change in placental vascular resistance (9) In fact it has been shown in pregnant rabbits that hypocapnia with arterial pO_2 maintained constant causes a major reduction of the maternal placental blood flow (21) Motoyama *et al* (30) found that induced maternal hypocapnia both in human and sheep reduced fetal arterial pO_2 In the converse experiments Dawes (9) kept the maternal oxygen tension constant in ewes and found that hypercapnia produced by administration of 3 10 per cent carbon dioxide raised the fetal pO_2 by 6-8 mm Hg which could not be accounted for by the Bohr shift

The observed effect on the FBM of lowered pCO_2 might therefore be elicited by dual mechanisms by reducing the uterine blood flow and by decreasing the CO_2 drive in the fetal respiratory regulation To these factors can also be added the influence of the secondary *hypoventilation causing maternal* hypoxaemia as evidenced by the fall in Tc pO_2 FBM have been shown to be abolished by induced hypoxaemia in sheep (3) and by hypoxaemia (and acidaemia) in women in labor (10) The relative importance of these mechanisms is still to be evaluated

Submitting the pregnant women to breathing *increased amounts of oxygen* we found a transient reduction of the incidence of FBM This response was

not accompanied by any effect on the maternal sys temic circulation or acid base balance The cause of the change of FBM is not obvious Discordant opin ions have been published about the effects of mater nal oxygen administration on fetal oxygenation Sa ling (34) found an increase in pre existing respiratory and metabolic acidosis in distressed fetuses after giv ing pure oxygen to the mother These results were not confirmed by Khazin *et al* (20) Observations during cesarean sections (33) and from several animal experi ments (1 8) suggest that an increase in maternal oxy gen tension causes only a disproportionally small in crease in fetal oxygen tension Among possible mech anisms for this discrepancy interest has been focused on the influence of hyperoxaemia on the blood flow to the pregnant uterus It would appear from the lit erature that the relation between maternal arterial pO_2 and uterine blood flow is not linear but depends on the absolute level of oxygenation (18) When stud ying in rabbits the most relevant fraction of uterine circulation i e the placental circulation Karlsson & Kjellmer (19) found a marked decrease in response to maternal hyperoxygenation It is doubtful whether the relatively small increase in maternal oxygen ten sion in the present work affected the placental perfu sion

ACKNOWLEDGEMENT

The authors thank Mrs Eva Eriksson Miss Ann Thuring and Mr Arne Bjuvholt for expert technical help We are grateful to colleagues from the Department of Clinical Physiology University of Lund Allmänna Sjukhuset Mal mö for laboratory analysis and valuable discussions

Supported by grants from the Swedish Medical Research Council (B77 17X-04517-03) the Swedish Tobacco Compa ny and the Medical Faculty of the University of Lund

REFERENCES

1 Assali N S Kirschbaum T H & Dilts P V Effects of hyperbaric oxygen on uteroplacental and fetal circu lation Circ Res *22* 573 1968
2 Boddy K & Robinson J S External method for de tection of fetal breathing in utero Lancet *2* 1231 1971
3 Boddy K Dawes G S & Robinson J S Intrauterine fetal breathing movements *In* Modern Perinatal Medi cine (ed L Gluck) p 381 Year Book Medical Pub lishers Chicago 1974
4 Boddy K & Dawes G S Fetal breathing Br Med Bull *31* 3 1975
5 Burton A C Physiology and Biophysics of the Circu lation p 86 Year Book Medical Publishers Inc Chicago 1965
6 Crawford J S Maternal hyperventilation and the foe tus Lancet *1* 430 1966
7 Curet I B Orr J A Rankin J H G & Ungerer T Effect of exercise on cardiac output and distribution of uterine blood flow in pregnant ewes J Appl Physiol *40* 725 1976
8 Dawes G S & Mott J C Changes in O_2 distribution and consumption in foetal lambs with variation in um bilical blood flow J Physiol *170* 524 1964
9 Dawes G S Foetal and Neonatal Physiology p 112 Book Medical Publishers Chicago 1968
10 Dawes G S Effects of fetal hypoxaemia on breathing movements and endocrine systems *In* Reviews in Peri natal Medicine (eds E M Scarpelli & E V Cosmi) p 333 University Park Press Baltimore 1976
11 Dejours P Control of respiration in muscular exer cise *In* Handbook of Physiology section 3 Respira tion Vol I (eds W O Fenn & H Rahn) p 631 Physi ological Society Washington D C 1964
12 Gennser G Marsál K & Brantmark B Maternal smoking and fetal breathing movements Am J Obstet Gynecol *123* 861 1976
13 Hohler C W Fox H E Yaeger H Inglis V & Steinbrecher M Real time B-scan observations Ef fect of maternal glucose on human fetal breathing *In* Ultrasound in Medicine Vol 3A (Clinical Aspects) (eds D N White & R E Brown) p 721 Plenum Press New York 1977
14 Hon E H & Wohlgemuth R The electronic evalua tion of fetal heart rate Am J Obstet Gynecol *81* 361 1961
15 Huch R Huch A & Lübbers D W Transcutaneous measurement of blood pO_2 (Tc PO)-method and ap plication in perinatal medicine J Perinat Med *1* 183 1973
16 Jacobson L Studies on acid base and electrolyte com ponents of human foetal and maternal blood during la bor p 32 Studentlitteratur Lund 1970
17 James S L & Indyk L Observation on fetal breath ing in baboons and lambs *In* Proceedings of Third Conference on Fetal Breathing (eds G Gennser K Marsal & T Wheeler) p 45 Malmö 1977
18 Karlsson K Intrauterine asphyxia An experimental study in rabbits and sheep with special reference to u terine blood flow and fetal cerebral reactions p 21 Thesis Gothenburg 1974
19 Karlsson K & Kjellmer I The uterine and maternal placental blood flow during hyperoxia J Perinat Med *2* 170 1974
20 Khazin A F Hon E H & Hehre F W Effects of maternal hyperoxia on the fetus 1 Oxygen tension Am J Obstet Gynecol *109* 628 1971
21 Leduc B The effect of hyperventilation on maternal placental blood flow in pregnant rabbits J Physiol *225* 339 1972
22 Lind A R Taylor S H Humphreys P W Kenelly B M & Donald K W The circulatory effects of sus tained voluntary muscle contraction Clin Sci *27* 229 1964
23 Lumley J Renon P Newman W & Wood C Hy perventilation in obstetrics Am J Obstet Gynecol *103* 847 1969

24 Mantell C Human fetal breathing The effect of altering maternal CO_2 level *In* Proceedings of Third Conference on Fetal Breathing (eds G Gennser K Marsal & T Wheeler) p 49 Malmö 1977
25 Maršál K Gennser K & Ohrlander S Fetal and neonatal breathing movements in man after betamethasone Life Sci *17* 449 1975
26 Maršál K Gennser G Jönsson S & Löfgren O Maternal work load and fetal breathing movements *In* Proceedings of Third Conference on Fetal Breathing (eds G Gennser K Maršál & T Wheeler) p 51 Malmö 1977
27 Marsál K Gennser G & Kullander S Intrauterine breathing movements and fetal presentation Obstet Gynecol *51* 163 1977
28 Martin C B Jr Murata Y Ikenone T & Ettinger B B Effect of alterations of pO_2 and pCO_2 on fetal breathing movements in Rhesus monkeys Gynecol Invest *6* 74 1975
29 Morris N Osborn S B Wright H P & Hart A Effective uterine blood flow during exercise in normal and pre-eclamptic pregnancies Lancet *2* 481 1956
30 Motoyama E K Rivard G Acheson F & Cook C D Adverse effect of maternal hyperventilation on the foetus Lancet *1* 286 1966
31 Parmelee A H Stern E & Harris M A Maturation of respiration in prematures and young infants Neuropadiatrie *3* 294 1972
32 Pomerance J J Gluck L & Lynch V A Maternal exercise as a screening test for uteroplacental insufficiency Obstet Gynecol *44* 383 1974
33 Rorke M J Davey D A & DuToit H J Foetal oxygenation during caesarean section Anaesthesia *23* 585 1968
34 Saling E Die Wirkung einer O_2-Atmung der Mutter auf die Blutgase und den Säure Basen Haushalt des Feten Geburtsh Frauenheilk *23* 528 1963
35 Saltin B & Stenberg J Circulatory response to prolonged severe exercise J Appl Physiol *19* 833 1964
36 Scarpelli E M Condorelli S & Cosmi E V Cutaneous stimulation and generation of breathing in the fetus Pediat Res *11* 24 1977
37 Sterky G Swedish standard curves for intra uterine growth Pediatrics *46* 7 1970
38 Wulf H The oxygen and carbon dioxide tension gradients in the human placental at term Am J Obstet Gynecol *88* 38 1964

Submitted for publication October 28 1977

Karel Maršál M D
Department of Obstetrics and Gynecology
Allmänna Sjukhuset
S-214 01 Malmö
Sweden

Acta Obstet Gynecol Scand 58 343–346 1979

FOLIC ACID SUPPLEMENT AND INTRAUTERINE GROWTH

J Rolschau J Date and K Kristoffersen

From the Departments of Obstetrics and Gynecology and Clinical Chemistry Odense University Hospital Odense Denmark

Abstract The effect of a folic acid supplement on birth weight and placental weight in women delivering in the early summer in Denmark was investigated

Thirty six women with normal pregnancy and expected delivery in the first half of June were selected consecutively They were paired two and two and allotted to two groups one of which was supplied daily with 5 mg folic acid and the second with tablets without folic acid from the 23rd week of pregnancy A significant correlation was found between erythrocyte folic acid and birth weight The infants in the folic acid group were 12 7 per cent heavier than those in the control group ($p<0\ 01$) A similar difference was found with regard to placental weight and the number of placental cells

The potential role of folic acid in pregnancy is obvious Metabolites of folic acid are necessary for the formation of nucleic acids and with this growth The best parameter of available folic acid is the content of the compound in erythrocytes (7) This content falls throughout pregnancy (2 6) the dosage of folic acid required to prevent this fall is the subject of controversy a review has been given by Rothman (18) It has recently been shown that folic acid improves the weight increase of erythroblastic infants during the first months of life (5)

A significant reduction in the number of placental cells was found in the period May June compared to August September during a prospective investigation carried out in Odense Denmark in 1972 73 The corresponding reduction in fetal weight was 6-7 per cent It was presumed that this was due to a variation in the amount of folic acid available to the infant in accordance with the following considerations The main source of folic acid apart from that present in the liver is uncooked green vegetables these first become common in the month of May in the northern countries The placenta of women to be delivered in June have ceased growth at this time (16) and the depots of folic acid have fallen to their minimum level

It was therefore considered possible to demonstrate folic acid deficiency in the early summer in Denmark by a prospective controlled trial

PATIENTS AND METHODS

Forty women in the 21st to 25th week of pregnancy were selected to take part in the trial They were taken consecutively from those attending the antinatal clinic of the Odense University Hospital and the only criteria employed were Danish birth and a normal pregnancy All of them were to be delivered between the 1st and 15 of June and the prediction of the term was reliable They were matched as well as possible two and two according to parity tobacco consumption prepregnant weight housing conditions and age Thereafter they were allotted to two groups The first was given tablets containing ordinary vitamins 250 mg ferrofumarate and 5 mg folic acid (the tablets were kindly supplied by Ferrosan A/S Copenhagen) indies The second group was supplied with similar tablets but without folic acid

Two of the women were taking no vitamines at the time of entering the trial Forty per cent of the others were taking tablets containing 0 1 mg folic acid This medication was replaced by the above regime The women were instructed to eat sufficient food and forbidden to take any other medication than the tablets supplied

Four refused to complete the trial One was erroneously given the wrong tablets and had therefore to be transferred from the second to first group The group given folic acid thereafter consisted of 20 and the other group of 16 women The trial was carried out as a blind investigation after the first consultation both in respect of the patients and investigators

Venous blood samples were withdrawn on the day before the trial commenced and one or two days after delivery

The folic acid content of serum and erythrocytes was determined by a competitive protein binding assay (15 17) Pteroylglutamic acid was used as the standard The day to day coefficient of variation was 0 03

The infants were weighed to the nearest 50 g The placenta were freed from membranes and the umbilical cord gently squeezed while being washed with physiological saline weighed and frozen The placentae were then homogenized and the content of nucleic acid determined as described elsewhere (16) The day to day coefficient of variation including the sampling error was 0 10

RESULTS

It can be seen from Table I that the average gestational age was identical in the two groups namely 281 days The average fetal weight was 407 g or 12 7 per cent higher in the folic acid group than in the control group this difference was statistically significant

Table I *Differences between folic acid supplement group and the control group in respect of gestational age, birth weight placental weight and content of RNA and DNA Student s unpaired test*

		N	Mean	SD±	t value	df	Significance	% difference
Gestational age	+ folic acid	20	281	11	0 13	34	NS	0 2
	− folic acid	16	281	14				
Birth weight	+ folic acid	20	3610	374	2 99	34	$p<0\ 01$	12 7
	− folic acid	16	3203	444				
Placental weight	+ folic acid	20	459	93	1 75	34	$p<0\ 1$	11 9
	− folic acid	16	410	68				
Placental RNA	+ folic acid	19	822	208	1 73	32	$p<0\ 1$	14 4
	− folic acid	15	718	114				
Placental DNA	+ folic acid	19	712	157	1 40	32	NS	11 1
	− folic acid	15	641	132				

The placental weight was on average increased by 11 9 per cent the RNA content by 14 4 per cent and the DNA by 11 1 per cent (these differences were not statistically significant) The same results were obtained with the non parametric Mann Whitney test

A significant correlation between erythrocyte folic acid concentration of the mothers at birth and birth weight was demonstrated when the two groups were combined (Table II) There was also a tendency towards a positive correlation to placental weight placental RNA and placental DNA although this was not statistically signficant The same applied to a correlation between plasma folic acid concentration at and birth weight placental weight RNA and although the correlation coefficients were

igure 1 shows the average plasma folic acid and erythrocyte folic acid prior to the commencement of the trial and at delivery for both groups There was no significant difference between the two groups before the start of the trial The plasma folic acid was 105 per cent higher at delivery in the folic acid group than in the control group ($t=13\ 9$ $p<0\ 001$ using the unpaired t test) Similarly the erythrocyte folic acid at birth was 34 per cent higher in the folic acid group than the control group ($t=8\ 5$ $p<0\ 001$) The sign test (19) demonstrated that there was a significant rise in plasma folic acid in the folic acid group and also that there was a significant fall in the control group The erythrocyte folic acid rose signficantly in both groups

The object and set up of the investigation was to elucidate the effect of a folic acid supplement to pregnant women No other factors were found which could explain the differences between the two groups

No differences were found in the following parameters Parity tobacco consumption prepregnant weight housing conditions age social status leucocyte count, mean erythrocyte volume mean erythrocyte hemoglobin concentration s transferrin and s-cobalamine

The weight increase of the mothers during pregnancy was 1 7 kg greater in the folic acid group than in the control group this was not significant The hemoglobin concentration in the folic acid group was 7 52 mmol/l and in the control group 7 92 mmol/l (non significant) There was no significant difference between the sexes of the newborn infants in the two groups in the folic acid group there were 40 per cent males in the control group 56 per cent

DISCUSSION

The present investigation has shown that the fetal weight placental weight and placental content of cells increased by 11 per cent to 12 per cent in the group of Danish women given a supplement of folic acid This is consistent with the findings in an intervention trial in a poor Indian population (12)

Table II *The two groups combined Correlation between erythrocyte folic acid at birth and birth weight placental weight and placental RNA and DNA*

	N	Correlation coefficient	Significance
Birth weight	35	0 53	$p<0\ 001$
Placental weight	35	0 32	$p<0\ 1$
Placental RNA	34	0 28	$p<0\ 1$
Placental DNA	34	0 22	NS

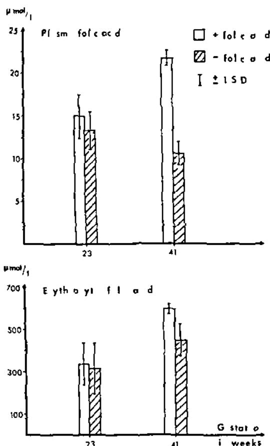


Fig 1 Average concentrations of serum folic acid and erythrocyte folic acid when trial started in the 23rd week and at delivery in the 41st week The average concentrations are depicted for the folic acid supplement group and the control group

and among Bantu negro women in Africa (1) In the latter trial there was no demonstrable effect of folic acid on a well nourished white population however no information was given in the report as to the season of the year in which the trial took place Lillie (13) stated from a non controlled study that a supplement of folic acid reduces the small for date rate Hibbard (11) found that 49 per cent of mothers giving birth to small for date infants had low erythrocyte folic acid Chanarin *et al* (2) found in a developed country that there was no correlation between erythrocyte folic acid and fetal weight Further Fletcher *et al* (4) found no effect of a supplement of folic acid on the fetal weight and placental weight however they did not mention the season in which the study was carried out

It is surprising that it was possible to demonstrate an increase in fetal and placental weight following a supplement of folic acid in Denmark where the population is considered to be homogeneous and well nourished Two factors are of importance in this respect firstly that Denmark is a northern country where uncooked green vegetables are uncommon during the winter months and in the spring This seasonal variation has been demonstrated in a number of studies Zachau Christiansen *et al* (22) found a low blood folic acid in the period February to April in Denmark and Yusufji *et al* (21) demonstrated a low serum folic acid during the month of April in India Other investigators (2 20) have observed a higher incidence of megaloblastic anemia in the winter Secondly the dietary habits are presumably different in northern areas to those in other parts of the world A low consumption of folic acid was found in similar geographical areas by several investigators (3 8 9 10)

However Martinez & Roe (14) have recently found that free folic acid intake was almost the same in winter and summer in New York

It should be noted that the effect of folic acid on intrauterine growth must be due to a folic acid deficiency and that this has been demonstrated among pregnant women giving birth in the early summer in Denmark In the event of this effect being confined to a few months only one would still expect it to reduce the rate of small for date infants

ACKNOWLEDGEMENTS

The authors wish to express their gratitude to J Ellegaard dr med Århus for his valuable advice and to Professor J Fabricius dr med Odense for his help in the statistical analyses We are also indebted to the staff and technical personal of the Institute of Pathology Odense University for their help in performing the analyses Ferrosan A/S Copenhagen kindly produced all the tablets used in the trial

REFERENCES

1 Baumslag Naomi Edelstein T & Metz J Reduction of incidence of prematurity by folic acid supplementation in pregnancy Br Med J *1* 16 1970
2 Chanarin I Rothman Doreen Ward Audrey & Perry Janet Folate status and requirement in pregnancy Br Med J *2* 390 1968
3 Ellegaard J Funktionel folinsyremangel p 116 Thesis Aarhus Denmark 1972
4 Fletcher J Gull A Fellingham F R Pranherd T A J Brant H A & Menzies D N The value of folic acid supplements in pregnancy J Obstet Gynaecol Br Comm 78 781 1971

5 Gandy Gillian & Jacobson W Influence of folic acid on birht weight and growth of the erythroblastotic infant Arch Dis Child 52 16 1977
6 Hansen H A Folic acid B_{12} vitamin und serum Fe under den normale graviditeten Nord Med 61 842 1959
7 Hansen H A On the diagnosis of folic acid deficiency Acta Obstet Gynecol Scand Suppl 7 13 1966
8 Helms P Kostundersøgelse i et plejehjem Ugeskr Laeg 139 815 1977
9 Herbert V Colman N Spivack M Ocasio E Ghanta V Kimmel K Brenner L Freundlich Joanne & Scott J Folic acid deficiency in the United States Folate assays in a prenatal clinic Am J Obstet Gynecol 123 175 1975
10 Hessov I & Elsborg L Folinsyre og B_1 vitaminind tagelse hos ældre patienter på en kirurgisk afdeling Ugeskr Laeg 139 825 1977
11 Hibbard B M Folates and the fetus S Afr Med J 49 1223 1975
12 Iyengar Leela & Rajalakshmi K Effect of folic acid supplement on birth weights of infants Am J Obstet Gynecol 122 332 1975
13 Lillie E W Obstetrical aspects of megaloblastic anaemia of pregnancy J Obstet Gynaecol Br Commonw 69 736 1962
14 Martinez Olga & Roe Daphne A Effect of oral contraceptives blood folate levels in pregnancy Am J Obstet Gynecol 128 255 1977
15 Mortensen E Determination of erythrocyte folate by competitive protein binding assay preceded by extraction Clin Chem 22 982 19 6
16 Rolschau J A prospective study of the placental weight and content of protein RNA and DNA Acta Obstet Gynecol Scand Suppl 72 28 1978
17 Rothenberg S P A radioimmunoassay for serum folate use of a twophase sequential incubation ligand binding system N Engl J Med 286 1335 1972
18 Rothman Doreen Folic acid in pregnancy Am J Obstet Gynecol 108 149 1970
19 Siegel S In Nonparametric statistics p 68 McGraw Hill Book Company Inc New York 1956
20 Thompson R B Seasonal incidence of megaloblastic anaemia of pregnancy and the puerperium Lancet 1 1171 1957
21 Yusufji D Mathan V I & Baker S J Iron folate and vitamin B_{12} nutrition in pregnancy a study of 1 000 women from southern India Bull WHO 48 15 1973
22 Zachau Christiansen B Hoff Jørgensen E & Østergård Kristensen H P The relative haemoglobin iron vitamin B_{12} and folic acid values in the blood of mothers and their newborn infants Dan Med Bull 9 157 1962

Submitted for publication February 2 1978

J Rolschau M D
Department of Obstetrics and Gynecology
Odense University Hospital
5000 Odense C
Denmark

Acta Obstet Gynecol Scand 58 347–351 1979

PREGNANCY COMPLICATIONS FOLLOWING CONIZATION OF THE UTERINE CERVIX (II)

Tom Weber and Erik B Obel

From the Department of Obstetrics and Gynecology YA and YC University of Copenhagen Copenhagen Denmark

Abstract The effect of conization upon the course of pregnancy and the fertility has been evaluated 44 women had a total of 66 pregnancies following conization These 44 women were compared with an age matched group of non conized women as well as with a group of non-conized women matched for both age and parity

There were more smokers among conized than among non-conized women All other descriptive variables were found to be without significant differences between the groups compared

There was no significant difference in the frequency of spontaneous and induced abortion prematurity or cesarean section between conized and non-conized women The second stage of labor was found to be protracted in conized women

Fertility judged by the latent period the time elapsed from the couple started sexual intercourse without use of contraception to the present pregnancy showed no difference between conized and non-conized women

We conclude that although a greater number of patients is necessary to permit definite conclusions concerning the risk of pregnancy and delivery complications in conized women it is of special interest that the present study did not demonstrate an increased risk of spontaneous abortion nor of prematurity

Since Miller & Todd (16) described 15 pregnancies following conization the difference of opinion has been very strong as to its possible effect on subsequent pregnancies (1 21)

The most important sequelae following conization were considered to be a possible increased risk of late abortion and premature delivery It has never been demonstrated definitely however if the risk was factual or not and there seem to be no comparative studied trying to evaluate the problem (21)

Because of controversial statements and missing documentation we have compared the course of pregnancy in conized women with that in non-conized women

MATERIAL AND METHODS

During the period 1 4 1974 to 31 12 1975 7 327 women were registered for delivery at Fredriksberg Hospital and Rigshopitalet At their first contact with the antenatal clinics all patients were interviewed by specially employed and trained staff 44 stated a previous conization All 7 327 women were interviewed about age previous pregnancies and their outcome education employment and smoking habits Later on a precoded questionnaire was completed for each patient based on the hospital record of the patient giving information concerning the course of actual pregnancy Besides in a special form is stated indi ation of conization ensuing acute complications following the operation and possible other cervical lesions Furthermore registration was made of all vaginal examinations during pregnancy admittance to hospital during preenancy or application of cerclage as well as gestational age at rupture of membranes and at delivery

As 17 of the 44 women had had one or more pregnancies between the conization and the actual pregnancy we have tried to evaluate the possible effect of conization on subsequent pregnancies as described below using the technique of mathed pairs

(1) The course of the actual pregnancy in conized women was compared with an age-matched group selected among all other patients

(2) The same examination as in point 1 but only patients *with no pregnancies between conization and the actual pregnancy* were taken into the analysis

(3) The *first pregnancy* following conization was compared with the course of pregnancy in women matched in such a way that they were of *same age and parity* at the time of conception (Example A 38 years old conized woman had the cone biopsy made when she was 30 years old At the first subsequent pregnancy she was 32 By then 2 parae This patient was matched with a 32 years old 2 parae non-conized woman)

(4) The *first pregnancy* following conization was compared with the first pregnancy after the same date in the *aged matched* women

(Example A 38 years old conized patient had the cone biopsy made July 1970 The first pregnancy after July 1970 is registered for the conized as well as the age matched woman)

Table I *Forty four coni.ed women and an age matched control group grouped according to the employment and educational level of the woman and her partner and to smoking habits*

	Conized	Age matched	p-value[c]
Woman s employment			
1 + 2 + 3 + 8	11/39	13/36	
4 + 5	21/39	17/36	0 76
6 + 7	7/39	6/36	
Partner s employment[a]			
1 + 2 + 3 + 8	14/44	20/44	
4 + 5	25/44	20/44	0 42
6 + 7	5/44	4/44	
Woman s education[b]			
1	14/44	11/44	
2	24/44	26/44	0 77
3	6/44	7/44	
Partner s education[b]			
1	18/44	13/44	
2	18/44	17/44	0 29
3	8/44	14/44	
Smoking (No of cigarettes/day)			
0	11/44	28/44	
1 – 5	7/44	4/44	
6 – 10	12/44	6/44	
More than 10	14/44	5/44	0 002

[a] 1+2+3+8 Professionals teachers managers nurses students
4+5 Off e staff skilled w rkers
6+7 Semi skilled workers unskilled workers

[b] 1 Only minimum education
2 *Intermediate edu ation*
3 H gher ed cation

lues ind ate differen es between the distribut ons among red/non on zed omen

ourse of *all pregnancies* before as well as after the zation was registered Then the course of pregnancies in the age matched control group *before and after the same* date as the conization was registered The course of pregnancy before and after conization were then compared with the course of pregnancy before as well as after the date of conization in non-conized control patients (Example 2 matched women at 38 The conized woman had the cone biopsy made July 1970 All pregnancies before and after *July 1970 were registered in the conized as well as the age* matched woman)

By the five methods above it is our intention to evaluate if the prognosis is changed for the total number of pregnancies following conization the first pregnancy following conization and the up till now last pregnancy following conization By the matching procedure described we have attempted to set up representative control groups

STATISTICS

The marginal distributions were tested by χ^2-test and 5 per cent regarded as significance level When the expected number of the individual categories was below 5 Fischer s exact test was adopted and 2 5 per cent regarded as *signficance level* as the test is one tailed

Table II *Forty four coni ed women and an age-matched control group grouped according to the number of previous pregnancies induced abortions parity birth weight of a previous infant and gestation at the end of a previous pregnancy*

	Conized	Age-matched	p-value
No of pregnancies before actual pregnancy			
0	6/44	12/44	
1	16/44	16/44	
2	13/44	11/44	
More than 2	9/44	5/44	0 34
Induced abortion before actual pregnancy			
Yes	12/44	5/44	
No	32/44	39/44	0 06
No of induced abortions before actual pregnancy			
0	30/34	34/44	
1	10/44	7/44	
More than 1	4/44	3/44	0 63
No of deliveries before actual pregnancy			
0	13/44	16/44	
1	22/44	20/44	
More than 1	9/44	8/44	0 79
Birth weight of previous infant			
0 – 2500 g	2/30	1/26	
More than 2500 g	28/30	25/26	0 55
Gestation of previous pregnancy (excl induced abortions)			
0 – 12 weeks	4/27	6/30	
13 – 27 weeks	3/27	2/30	
28 – 35 weeks	1/27	1/30	
More than 35 weeks	21/27	21/30	0 90

RESULTS

The descriptive variables of the conized women and their age matched controls are compared in table I and II Course of pregnancy is indicated in table III IV and V Fertility following conization is evaluated in table VI

Table I indicates that there is no difference between the social status and educational level of the conized women and their age matched controls But the number of heavy smokers is significantly greater in the conized group ($p = 0\ 002$)

Table II demonstrates that there is no difference between the conized patients and their age-matched controls as regards distribution of pregnancies spontaneous abortions and deliveries before the actual pregnancy There seems to be a tendency however towards an increased rate of induced abortions among the conized women as compared with their age matched controls But the difference is not significant ($p = 0\ 06$)

Table III *The number of spontaneous abortions induced abortions low birth weight infants and of Caesare an sections in conized and non conized women compared according to the methods described*

Method No	Early abortion (before 13 week) No	p-value	Induced abortion No	p-value	Late abortion (after 12 week) No	p-value	Premature delivery (< 2501 g) No	p-value	Caesarean section/ No of deliveries no	p-value
1 Conized women Age matched group					3/44 1/44	0 31	5/41 1/41	0 09	8/41 5/43	0 32
2 1 st preg foll coniz Age matched controls					2/27 1/27	0 50	1/25 1/26	0 75		
3 1 st preg foll coniz Age and parity matched group					3/34 0/43	0 08	1/31 1/43	0 67		
4 1 st preg foll coniz Age matched group	6/44 3/44	0 24	3/44 1/44	0 31	3/34 1/40	0 25	1/31 1/39	0 69		

Table II also indicates the frequency of prematurity judged by birth weight below 2 501 grams at the pregnancy prior to the actual one There is no difference between the groups Besides table II states the gestational age at the termination of the previous pregnancy distributed on early and late abortions and premature as well as term deliveries all cases of induced abortion being omitted There is no difference between the distributions of these two groups

Table III and IV evaluates the course of one or more pregnancies following conization according to the above five methods

When using method No 1 there is a tendency towards an increased rate of prematurity at the last (actual) delivery But this tendency is not statistically significant ($p = 0\ 09$) and is not seen by the other methods (2 5)

Method No 3 demonstrates a non significant tendency towards an increased rate of late abortions among conized women ($p = 0\ 08$) The other methods do not reveal the same tendency

The frequency of early abortion induced abortion and cesarean section is not changed in any case when comparing conized women with their age-matched controls

Table V demonstrates a tendency towards an increase of not planned pregnancies among the conized women ($p = 0\ 05$) and that a significantly greater number were hospitalized during pregnancy' Considering the small number of patients we also found more women in the conized group with an elongated (more than 30 minutes) secondstage labor ($p = 0\ 04$) This factor reappears without being significant when considering only the first postconization pregnancies (method 2)

Table VI shows the fertility evaluated by the time elapsed from the couple started sexual intercourse without use of contraception to the actual pregnancy (latent period) There is no difference between the

Table IV *The outcome of all pregnancies before and after the date of conization in conized women and in an age matched control group (Method No 5)*

	Conized Before conization a	Conized After conization b	Age matched Before time of coniz c	Age matched After time of coniz d	p(a/b)	p(c/d)	p(a/c)	p(b/d)
Early abortion	12/54	8/66	8/50	5/55	0 11	0 22	0 29	0 41
Induced abortion	7/54	5/66	3/50	1/55	0 25	0 27	0 19	0 15
Late abortion (> 12 w of gest)	0/35	4/52	3/39	1/49	0 12	0 23	0 14	0 [illegible]0
Premature delivery (< 2501 g)	4/35	5/48	3/36	1/48	0 58	0.21	0 48	0 10
Total No of pregnancies	54	66	50	55				

Table V *The number of planned pregnancies women bleeding before 28 weeks of gestation women hospitalized during pregnancy women with insufficiency of the cervix and women with a second stage of labor more than 30 minutes in conized and non conized women compared accoeding to the methods described*

Method No	Pregnancy not planned No	p-value	Bleeding before 28 week of gest No	p-value	Hospitalized during pregnancy No	p-value	Cervical insufficiency No	p-value	2 nd stage > 30 min no	p-value
1 Conized women Age matched group	16/44 8/44	0 05	10/44 6/44	0 27	13/44 5/44	0 03	3/44 0/44	0 12	8/32 2/33	0 04
2 1 st preg foll coniz Age matched controls	9/27 4/27	0 11	5/27 2/27	0 21	7/27 3/27	0 16	1/27 0/27	0 50	4/17 0/18	0 05

conized women and their age matched controls but this factor was evaluated for 21 and 20 respectively of the two groups

DISCUSSION

The course of pregnancy in conized women has been compared with that of their age matched controls Besides the course of pregnancy in conized women was compared with a control group also matched for parity Table I and II indicate that the groups were comparable as regards the descriptive variables mentioned only heavy smokers were found more frequently in the conized group than in the controls

By method No 1 3 (see above) it has been possible evaluate the risk of prematurity among conized as compared with a control group (table III) No 1 3 could not be used for an evaluation he frequency of induced abortion and early as well as late abortion as very often either the conized patients or their controls were not registered at the antenatal clinics till after 20 week of gestation (only 30 per cent were registered before 16 weeks of gestation) In contrast by method No 4 (table III) about half the pregnancies had been terminated before the actual interview so an evaluation of an altered abortion rate following conization was possible here This was also the case by method No 5 where further more the number of pregnancies was increased

A lesion of the uterine cervix following conization might be expected to result in cervical insufficiency with an ensuing risk of late abortion and prematurity In spite of the large number of smokers among conized women none of the five methods could demonstrate an increased risk of premature infants following conization Only method No 1 had a tendency towards increased prematurity ($p = 0\ 09$) but this tendency disappears if we exclude from the conized group the only patient with a high cone biopsy who delivered a premature infant of 1 400 grams There was no increased risk of late abortion in this material as the tendency revealed by method No 3 ($p = 0\ 08$) is not demonstrated by the other methods (see table III and IV)

Some papers record an increased frequency of induced abortion (19 20) and early abortion (3 4 5 7 12) following conization The present paper did not arrive at the same result (table III and IV)

The increased rate of unwanted pregnancies following conization (4 5 8 20) as recorded by other papers is in the present study evaluated by the frequency of not planned pregnancies In our material (table V) this frequency is increased following conization ($p = 0\ 05$) A possible explanation might be that the patients do not know that fertility is normal following conization

The increased rate of hospitalized conized pregnant women is probably due to medical over-care especially as a short collum is difficult to distinguish from an initiating cervical insufficiency

In literature is recorded cases of cervical stenosis (2 7 14 15) as well as a tendency to precipitated delivery (2 5) In the present material there was a greater number of women among the conized women among age-matched controls with a protracted second stage of labor (table V) We attempted to

Table VI *The time elapsed (in months) from the couple started sexual intercourse without use of contraception to the actual pregnancy in conized women and in age matched control group*

Group	0–3	0–6	0–9	0–12	0–24
Conized women	10/21	12/21	14/21	14/21	18/21
Age matched group	9/20	11/20	13/20	14/20	18/20

evaluate the dilatation period by recording vaginal examinations during first stage but the examinations were too few to permit an evaluation

Literature reports have very inconsistent indications regarding postconization fertility (4 5 7 8 9 10 12 15 17 19 20) Most studies find however that conization has no effect on fertility (7 8 9 10 12 15 17 19 20) In this study we only evaluated fertility by the latent period which could not be correlated with conization

It was in this paper not possible to evaluate if the conization method adopted has any effect on subsequent pregnancies as most operation records do not indicate size of cone nor technique adopted In this material we had only one case of high cone biopsy performed in a woman with carcinoma in situ of the uterine cervix The subsequent (and till now last) pregnancy of this woman ended in a premature delivery at 28 weeks of gestation of an infant of 1 400 grams

CONCLUSIONS

The methods adopted in the present paper did not demonstrate that the prognosis of pregnancies in a group of conized women should be inferior to that of a comparable group of non-conized women The material was however very small and further studies with larger patient materials are required before decisive statements as to the prognosis of pregnancies following conization can be made In view of the actual material we find that a possible individual risk of a slightly increased rate of abortion or premature delivery following conization is so small that it is of no real importance

Judged by the latent period we did not demonstrate reduced fertility following conization in our material

REFERENCES

1 Baradlai Bank E Die Wirkung der Zervix Konisation auf die Fertilität und auf die Gestationsvorgänge Gynaecologia *149* 26 1960
2 Champion P K & Thompson N J Effect of conization of the cervix on subsequent pregnancy Am J Obstet Gynecol 62 1321 1951
3 Crossen R J Wide conization of cervix Am J Obstet Gynecol *57* 187 1949
4 Fettig O & Hillemanns H G Die Zervixkonisation Dtsch med Wsch *23* 1197 1962
5 Fettig O & Kühn C Konzeptionshäufigkeit Schwangerschafts und Geburtsverlauf nach Zervixkonisation Geburtsh Frauenheilk *23* 517 1963
6 Hittmair A Erfahrungen mit der Elektrokonisation der Portio Wien med Wschr *117* 855 1967
7 Holzer E Fertilität Schwangerschafts und Geburtsverlauf nach Konisation der Portio vaginalis uteri Geburtsh Frauenheilk *32* 950 1972
8 Kern G & Aslani A & Kern Bontke E & Gräfin zu Eulenburg H Folgen der Zervixkonisation Geburtsh Frauenheilk *27* 879 1967
9 Kullander S & Sjöberg N Treatment of carcinoma in situ of the cervix uteri by conization Acta Obstet Gynecol Scand *50* 153 1971
10 Kummert W Spätergebnisse nach diagnostischer und therapeuthischer Portiokonisation Zbl Gynäk *92* 1569 1970
11 Lemberger F Schwangerschaften nach Operationen der Portio Münch med Wschr *104* 1330 1962
12 Litschgi M & Benz J J Konisation und Fertilität Fortschr med *92* 1240 1974
13 McLaren H C Conservative management of cervical precancer J Obstet Gynaecol Brit Cwlth *74* 487 1967
14 McLaren H C Jordan J A & Glover M & Attwood M E Pregnancy after cone biopsy of the cervix J Obstet Gynaecol Brit Cwlth *81* 383 1974
15 McVicar J & Willocks J The effect of diathermy conization of the cervix on subsequent fertility pregnancy and delivery J Obstet Gynaecol Brit Cwlth *75* 355 1968
16 Miller N F & Todd O E Conization of the cervix Surg Gynec Obstet *67* 265 1938
17 Retsch H H & Wolff C Die therapeutische Elektrokonisation bei Frauen im fertilen Alter Geburtsh *Frauenheilk 25 553 1965*
18 Ryams M N A new instrument for excision of the diseased endocervix with surgical diathermy N Y State J Med *28* 646 1928
19 Tornai I & Klacsmann L Fruchtbarkeitsproblem nach Kollumrehabilitierung Zbl Gynäk *92* 1499 1970
20 Trnka V & Skoda V & Novotná J Der Einfluss der Amputation und der Konisation der Portio vaginalis uteri auf die Fertilität und den Schwangerschaftsverlauf Geburtsh Frauenheilk *28* 1011 1968
21 Weber T & Obel E B Pregnancy complications following conization of the uterine cervix (I) Acta Obstet Gynecol Scand *58* 259 1979

Submitted for publication 27 October 1977

T Weber M D
Department of Obstetrics and Gynecology YA YC
Rigshospitalet
DK 2100 Copenhagen
Denmark

Table V *The number of planned pregnancies women bleeding before 28 weeks of gestation women hospitalized during pregnancy women with insufficiency of the cervix and women with a second stage of labor more than 30 minutes in conized and non-conized women compared accoeding to the methods described*

	Pregnancy not planned		Bleeding before 28 week of gest		Hospitalized during pregnancy		Cervical insufficiency		2 nd stage > 30 min	
Method No	No	p-value	No	p-value	No	p-value	No	p-value	no	p-value
1 Conized women Age matched group	16/44 8/44	0 05	10/44 6/44	0 27	13/44 5/44	0 03	3/44 0/44	0 1?	8/32 2/33	0 04
2 1 st preg foll coniz Age matched controls	9/27 4/27	0 11	5/27 2/27	0 21	7/27 3/27	0 16	1/27 0/27	0 50	4/17 0/18	0 05

conized women and their age matched controls but this factor was evaluated for 21 and 20 respectively of the two groups

DISCUSSION

The course of pregnancy in conized women has been compared with that of their age matched controls Besides the course of pregnancy in conized women was compared with a control group also matched for parity Table I and II indicate that the groups were comparable as regards the descriptive variables mentioned only heavy smokers were found more frequently in the conized group than in the controls

By method No 1 3 (see above) it has been possible evaluate the risk of prematurity among conized n as compared with a control group (table III) d No 1 3 could not be used for an evaluation e frequency of induced abortion and early as well as late abortion as very often either the conized patients or their controls were not registered at the antenatal clinics till after 20 week of gestation (only 30 per cent were registered before 16 weeks of gestation) In contrast by method No 4 (table III) about half the pregnancies had been terminated before the actual interview so an evaluation of an altered abortion rate following conization was possible here This was also the case by method No 5 where furthermore the number of pregnancies was increased

A lesion of the uterine cervix following conization might be expected to result in cervical insufficiency with an ensuing risk of late abortion and prematurity In spite of the large number of smokers among conized women none of the five methods could demonstrate an increased risk of premature infants following conization Only method No 1 had a tendency towards increased prematurity ($p = 0\ 09$) but this tendency disappears if we exclude from the conized group the only patient with a high cone biopsy who delivered a premature infant of 1 400 grams There was no increased risk of late abortion in this material as the tendency revealed by method No 3 ($p = 0\ 08$) is not demonstrated by the other methods (see table III and IV)

Some papers record an increased frequency of induced abortion (19 20) and early abortion (3 4 5 7 12) following conization The present paper did not arrive at the same result (table III and IV)

The increased rate of unwanted pregnancies following conization (4 5 8 20) as recorded by other papers is in the present study evaluated by the frequency of not planned pregnancies In our material (table V) this frequency is increased following conization ($p = 0\ 05$) A possible explanation might be that the patients do not know that fertility is normal following conization

The increased rate of hospitalized conized pregnant women is probably due to medical over-care especially as a short collum is difficult to distinguish from an initiating cervical insufficiency

In literature is recorded cases of cervical stenosis (2 7 14 15) as well as a tendency to precipitated delivery (2 5) In the present material there was a greater number of women among the conized women among age matched controls with a protracted second stage of labor (table V) We attempted to

Table VI *The time elapsed (in months) from the couple started sexual intercourse without use of contraception to the actual pregnancy in conized women and in age matched control group*

Group	0–3	0–6	0–9	0–12	0–24
Conized women	10/21	12/21	14/21	14/21	18/21
Age matched group	9/ 0	11/20	13/20	14/ 0	18/ 0

Acta Obstet Gynecol Scand 58 353–360 1979

AMNIOTIC FLUID CELL EXFOLIATION IN EARLY HUMAN PREGNANCY

Staffan Bergström

From the Departments of Obstetrics and Gynecology and Human Anatomy University Hospital Uppsala and Department of Obstetrics and Gynecology Central Hospital Eskilstuna Sweden

Abstract An ultrastructural study of amniotic epithelium and fetal periderm was undertaken in order to investigate the exfoliative capacity in these tissue surfaces in early human pregnancy Contrary to earlier reports no exfoliation could be detected from amniotic epithelium while a heavy detachment of cells and cell fragments was observed from fetal skin The importance of meticulous tissue preparation is obvious detachment phenomena are easily produced artifactually by tissue scrapings and improper tissue preparation for morphological investigations

Since the discovery of the cells in amniotic fluid by Daniel (1) few studies on amniotic fluid have focussed on the clinical applications of amniotic fluid cytology Not until half a century after Daniel s paper was an attempt made to apply these cytological findings in the diagnosis of ruptured membranes (2) A decade later antenatal sex determination on the basis of amniotic fluid cytology was described by Rosa and Fanard (3) This achieved a breakthrough for cytodiagnosis by amniocentesis and a large number of publications have since described the antenatal diagnosis of several sex linked inherited diseases (for review see Fuchs and Cederquist (4))

Amniotic fluid cells constitute the earliest easily available tissue sample from the fetus carrying significant information on its chromosomal features In early pregnancy cytodiagnosis for genetic counselling is of primary concern while in late pregnancy cytodiagnosis is used almost exclusively for determination of fetal maturity Prematurity still plays an important role in neonatal mortality According to a recent study (5) in the U S more than 1 per cent of all neonates born alive develop RDS which still has a lethal outcome in about 30 per cent of cases

Cytodiagnosis if reliable would be a worhtwhile alternative to biochemical monitoring in testing for fetal maturity in risk cases e g with meconium contamination where the L/S ratio is less well related to maturity In an attempt to settle the question of reliability of cytodiagnosis in the determination of fetal maturity Morrison and co-workers (6 7) carried out critical studies on the methodology of amniotic fluid cytodiagnosis By carefully evaluating various steps in the cell preparation they demonstrated that a number of crucial details could explain the variation in reliability observed by several investigators utilizing the Nile Blue sulphate technique The cell pattern as an expression of fetal maturity accordingly became more important than before The origin of the maturity typical cell pattern is unknown and little is understood about the behaviour of tissue surfaces facing the amniotic cavity and their potential contribution to amniotic fluid cytology

The purpose of the present study was to investigate by scanning electron microscopy (SEM) the existence of exfoliative properties in the major components of the surface facing the amniotic fluid the amniotic epithelium and the fetal periderm In order to obtain extensive biopsies the study was limited to early pregnancy

MATERIAL AND METHODS

Amniotic sacs from 16-19 week pregnancies interrupted by hysterotomy for legal abortion were collected from 10 women and in the operation room immediately immersed in 2 5 per cent glutaraldehyde in Soerensen s phosphate buffer pH 7 4 Small specimens of reflected and placental amnion and from fetal periderm were cut and immersed in aliquots of glutaraldehyde in which they were kept until further processing After at least a few days in glutaraldehyde the specimens were rinsed in the same buffer postfixed in 1 per cent OsO_4 and subsequently rinsed in three consecutive baths of redistilled water Preparation for SEM was then carried out by freezing each specimen in a minute amount of redistilled water by dropping it in a quenching medium of iso-penthane cooled by liquid nitrogen (-196 C) Ensuing drying was then carried out at the temperature of dry ice for ~3 days Orientation and mounting on SEM stubs were then carried out before sputter coating with gold took place Observations were made in a Jeol JSM U3 scanning electron microscope run at 15-20 kV



Fig 1 Amniotic epithelium 19th week The bulging microvillous appearance of the epithelial cells is typical Note regular polygonal strands constituting intercellular borders No exfoliation SEM Magn 2 000 ×

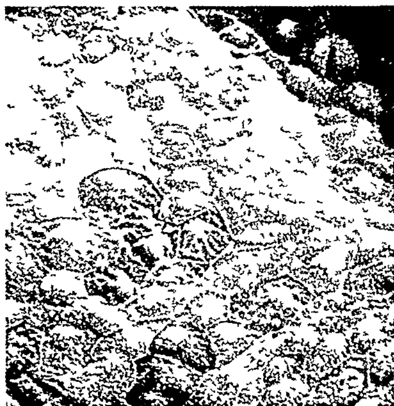


Fig 2 Survey over amniotic epithelium showing a few poorly microvillous epithelial cells obviously in a different phase of development from the cells adjacent to them SEM Magn 1 100 ×

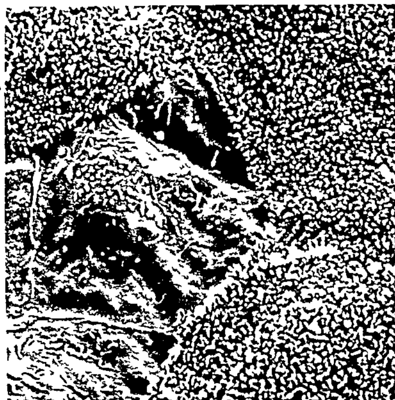


Fig 3 Close-up of Fig 2 demonstrating strikingly different surfaces of adjacent amniotic epithelial cells
SEM Magn 5 200 ×

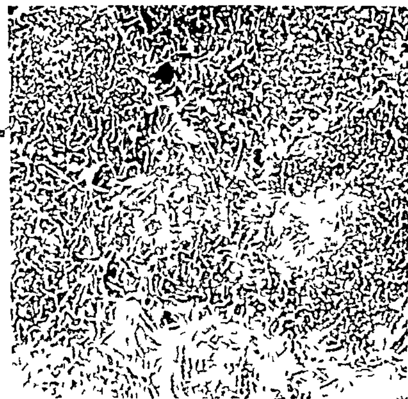


Fig 4 In most amniotic epithelial cells small holes in the three-cell junctions are seen Their function remains unclear but they have been regarded as a morphological correlate of the extensive turnover of amniotic fluid
SEM Magn 5 200 ×



Fig 5 Close up of intercellula canal between amniotic epitheli cells Detail of Fig 4 SEM Magn 43 000 ×

RESULTS

ion Both in reflected and in placental amnion um showed a homogeneous appearance 1) with somewhat convex polygonal cell sur densely populated by microvilli evenly distributed over the apical surface of the epithelium In some instances smooth non microvillous surfaces were encountered (Figs 2 3) but there were no signs of any detachment of cells from the amniotic epithelium In many areas intercellular spaces were conspicuous in the three cell junctions of intercellular borders (Figs 4-5)

Periderm In contrast to the inactive appearance of the amniotic epithelium the outermost layer of fetal skin displayed a marked activity of detachment of cells and cell fragments A series of events could be established elucidating the process whereby peridermal elements were liberated to the amniotic fluid Within a single cell surface various stages of detachment could be visualized and followed in detail The first visible event was a slight elevation of a limited portion of the apical surface area concomitant with the appearance on its surface of microvillous lining surrounded by a smooth area of non microvillous surface (Fig 6) The second event was the emergenc of minor indentations around the slightly elevate portion first like single holes later like minute spaces joining to form confluent larger spaces The third event was a more pronounced protrusion of the elevated part by a gradual pinching off effect at its base (Fig 6) The protrusion was thereby rendered less microvillous and sometimes displayed indentations also on its surface The fourth event was the very moment of cell detachment captured at the instant of exfoliation (Figs 7 8) Some areas were particularly rich in the detachment stages suggesting that at a given time certain areas but not others undergo exfoliation The cells liberated were ovoid or round in shape and covered with a thin lining of short microvilli Th stalks connecting the detaching cells to the underlying peridermal surface were fairly homogenous arou d 1 2 μ in diameter The fifth event was the disappearance of the cell and the remaining stalk (Fig 9) This presumably occurred immediately before a d st nct peridermal membrane reaction to the deta hment visible as a withdrawal of the stalk with the formation of a crater around the stalk (Fig 9 10)



Fig 6 Fetal skin surface 19th week A general tendency to exfoliation of cell fragments from each peridermal cell is apparent Note various stages in the exfoliation process The first stage is typically a barely visible elevation of a part of the cell surface characteristically microvillous (arrows) A more and more pronounced protrusion of the elevated part is seen prior to its final detachment from the surface The indentations (I) are seen in several fragments
SEM Magn 1 200 ×

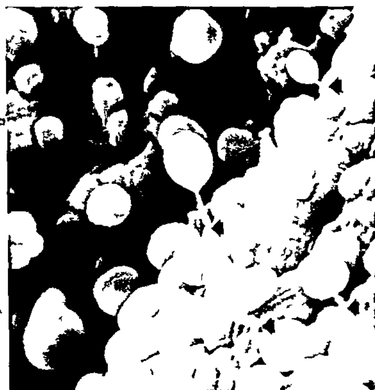


Fig 7 Exfoliation of cell fragment captured just at the detachment stage (arrows) Note stalks and microvillous surfaces of exfoliating fragments
SEM Magn 1 700 ×



Fig 8 Detail of Fig 7 The thin sta stemming from the mother cell is o viously stretched for a while before d tachment is finished
SEM Magn 5 000 ×

DISCUSSION

) cell content of amniotic fluid in early pregnancy is sparse In various studies the fluid has been described as virtually acellular prior to the 14th week (8) and even as late as the 25th week (9) Although general agreement exists regarding the scarcity of cells prior to the 16th week (10) there is evidence that cells and cell fragments make a significant contribution to the amniotic fluid during this period as shown in the present study Detached cells are regarded as viable at the moment of exfoliation but are presumably degenerating rapidly due to the presence of nuclear pycnosis and membrane bound structures similar to lysosomes (10)

Amniotic fluid cells obtainable by amniocentesis in early pregnancy are of two types The first most prevalent one is characterised by a dense microvillous lining on a round or oval outline covering a cytoplasm laden with a glycogen deposit which is heavier in younger specimens The second type has obviously phagocytotic capacity due to the contents of engulfed material (10) The first type of cell as described by Hoyes (10) is presumably identical to the cell exfoliated from the periderm as observed b SEM in the present study

The surface morphology of tissues facing the am niotic cavity has been subject to several investigatior since the classical studies of Bowen (11) The blad der cells discovered in the light microscope got a ultrastructural interpretation later and were found t appear during a limited period of human pregnanc from around the fourth up to the sixth month (12 As peridermal derivates of apparent function significance considering the extensive contributio of cell material from the fetus to the amniotic fluic these bladder cells have attracted astonishingly li tle attention Since they display an abundance c glycogen granules their presumed degeneration i believed to represent a contribution of glucose to am niotic fluid (10) It is not clear whether there is a ci culation of glucose between peridermal cells and am niotic fluid It has been suggested that the significar amounts of glucose in amniotic fluid around 200 m per liter (13) are taken up partly by the outermos peridermal cells to form the glycogen deposit visibl in the electron microscope (14) The steady state i amniotic fluid glucose concentration is obviousl



Fig 9 Two recently detached mother areas (arrows) showing remnants of the stalk connecting the detached cell fragment and the mother cell Note al o the microvillous areas presumably representing the cell membrane preparing itself for ensuing exfoliation
SEM Magn 1 700 ×



Fig 10 Detail of Fig 9 demonstrating the microvillous appearance of the cell membrane adjacent to the recently detached area To the left microvillous protrusions presumably loosely connected to underlying periderm and prepared to be detached to the amniotic fluid
SEM Magn 5 ?00 ×

maintained despite the extensive detachment of cell material demonstrated by SEM Hence this abundant contribution of glycogen to the fluid should involve a similar output of glycogen or glucose from the fluid either by reabsorption across the periderm or by alternate clearance routes

Amniotic epithelium was found by SEM not to contribute at all to the cell contents of amniotic fluid This is contrary to the belief of several earlier investigators (8 15 16 17 18 19) Most of these studies drew conclusions from scrapings of amniotic epithelium a method obviously open to the criticism of artefactual detachment of tissue fragments from non-exfoliating surfaces (20) The striking difference in the present study in appearance of amniotic epithelium and periderm respectively by SEM investigations on intact tissue surfaces underscores the risk of morphological conclusions from correlate studies involving delicate events that are easily deranged and interfered with by improper methodology

To conclude by SEM of intact surfaces of amniotic epithelium and fetal periderm in early pregnancy it was shown that an extensive contribution was obvious from the latter to amniotic fluid while virtually no detachment of cell material took place from the former contrary to earlier reports

ACKNOWLEDGEMENTS

[1] by grants from the Swedish Medical Research (B 78 17X) Stiftelsen Allmänna Barnbördshusets Minnesfond and Prenatalforskningsnämnden

REFERENCES

1 Daniel M C Recherches sur la cytologie du liquide amniotique Ann Gynécol Obstét *1* 466 1904
2 Bourgeois G A The identification of fetal squames and the diagnosis of ruptured membranes by vaginal smears Am J Obstet Gynecol *44* 80 1952
3 Rosa P A & Fanard A E A new method of prenatal diagnosis of sex Int J Sexol *4* 160 1951
4 Fuchs F & Cederqvist L Prenatal diagnosis based upon amniotic fluid cells *In* Amniotic fluid research and clinical application (eds D V I Fairweather and T K A B Eskes) p 262 Amsterdam Excerpta Medica 1973
5 Driscoll J M & Mellins R B Idiopathic respiratory distress syndrome Am Thoracic Soc *1* 5 1973
6 Morrison J C Morrison D L Lovett F A Whybrew W D Bucovaz E T Wiser W L & Fish S A Nile blue staining of cells in amniotic fluid for fetal maturity Part I A reappraisal Obstet Gynecol *44* 355 1974
7 Morrison J C Morrison D L Lovett F A Whybrew W D Bucovaz E T Wiser W L & Fish S A Nile blue staining of cells in amniotic fluid for fetal maturity Part II In complicated obstetric cases Obstet Gynecol *44* 362 1974
8 Wachtel E Gordon H & Olsen E Cytology of amniotic fluid J Obstet Gynaecol Brit Commonw *76* 596 1969
9 Marianowski L & Wacker Pujdak B Cytology of amniotic fluid in different periods of pregnancy Matern Med Pol *5* 203 1973
10 Hoyes A D Ultrastructure of the cells of the amniotic fluid J Obstet Gynaecol Brit Commonw *75* 164 1968
11 Bowen J T The epitrichial layer of the human epidermis Anat Anz *4* 412 1889
12 Hoyes A D Electron microscopy of the surface layer (periderm) of human fetal skin J Anat *103* 3?1 1968
13 de Miguel Adrián J M Gonzalez Batros C Garcia Perez M C Sáez Benito J & Gómez Calatayud M Bioquimica y citologia del liquido amniotico en el tercer trimestre de la gestación Acta Obstet Ginecol Hisp-Lusit *20* 313 1972
14 Serri F & Montagna W The structure and function of the epidermis Pediat Clin N Am *8* 917 1961
15 van Leeuwen L Jacoby H & Charles D Exfoliative cytology of amniotic fluid Acta Cytol (Baltimore) *9* 442 1965
16 Votta R A Bobrow de Gagneten C Parada O & Giuleitti M Cytologic study of amniotic fluid in pregnancy Am J Obstet Gynecol *10?* 571 1968
17 Casadei R D Ablaing G Kaplan B J & Schwinn C P A cytologic study of amniotic fluid Acta Cytol *17* 289 1973
18 Churchouse M J & Langstone V E The occurrence and origin of satellite cells in amniotic fluid (preliminary report) Acta Cytol *14* 609 1970
19 Morris H H B & Bennett M J The classification and origin of amniotic fluid cells Acta Cytol *18* 149 1974
20 Bergström S Ultrastructure of cell detachment from the human fetus in early pregnancy Acta Obstet Gynecol Scand in press 1979

Submitted for publication March 8 1978

Staffan Bergström M D
Department of Obstetrics and Gynecology
Central hospital
S 631 88 Eskilstuna
Sweden

Acta Obstet Gynecol Scand 58 361–364 1979

PLATELET FUNCTION COAGULATION AND FIBRINOLYSIS DURING TERMINATION OF MISSED ABORTION AND MISSED LABOR BY $PGF_{2}\alpha$ AND OXYTOCIN

R C Briel S Kunz and E Kidess

From the Department of Obstetrics and Gynecology Tübingen Germany

Abstract In cases of missed abortion and missed labor labor was induced by $PGF_{2}\alpha$ i a i v and by oxytocin infusion Platelet function (methods of Born and Breddin) the coagulation system and fibrinolysis have been studied within the three groups

Using $PGF_{2}\alpha$ i v the initially increased platelet aggregation showed a tendency to become normal There was no manifestation of activation of the coagulation system Fibrinolytic activity showed a slight increase during $PGF_{2}\alpha$ i v

No essential changes in platelet function coagulation and fibrinolytic system were found after i a injection of $PGF_{2}\alpha$

When inducing labor by oxytocin i v both the coagulation and the fibrinolytic system were slightly activated and platelet aggregation increased

The results and their clinical importance for hemostasis as well as therapeutic consequences are discussed

During induction of abortion by intra amniotic instillation of hypertonic sodium chloride solution alterations of the blood coagulation system are well known (13 21) There have been numerous reports of DIC the decrease and consumption of coagulation factors and hemorrhagic shock during this method of induction of abortion (3 19)

In cases of missed abortion with curettage an initial alteration of the coagulation system or an alteration which develops during and after the procedure is even more frequently found than in cases of therapeutic abortion (9 12 17)

As $PGF_{2}\alpha$ now becomes the preferred method for induction of labor in cases of missed abortion (m a) and missed labor (m l) (10 14) it seemed to be of interest and clinical importance to study the changes of some parameters of the coagulation and fibrinolytic system and of platelet function within this high risk group

MATERIAL AND METHODS

The following groups have been investigated
1 $PGF_{2}\alpha$ i v 0 05 mg/min (m a /m l) n=8
2 $PGF_{2}\alpha$ i a 40 mg (m a /m l) n=8
3 Oxytocin i v 30-40 mE/min (m l) n=7
Blood sampling was performed according to the following time schedule
0=before infusion or injection
I=1 hour after commencing treatment
II=4 hours after commencing treatment
III=1 day after evacuation of the uterus
The coagulation profiles performed consisted of
Thrombelastogram (TEG) (reaction time and maximal amplitude) and fibrinogen (measured as clottable fibrinogen Thyrosin Tryptophan method) (only cases of $PGF_{2}\alpha$ i v)
platelets (coulter counter)
Antithrombin III (AT III) (radial immunodiffusion Mancini technique)
Parameters of fibrinolysis
Plasminogen (Mancini technique) Fibrin Fibrinogen degradation products (FDP) (staphylococcal clumping test) α_1 Antitrypsin (α_1 AT) and α_2 Macroglobulin (α_2 MG) (Mancini technique)

Studies on platelet function were performed according to a standardized time procedure (Fig 1) using the following methods
1 ADP and collagen induced platelet aggregation by the photometrical method of Born (4)
2 Platelet aggregation test (PAT) by Breddin (5) Statistical evaluation t paired Because of the great interindividual differences of the initial values of the groups we didn t give the standard deviation (SD)

RESULTS

Coagulation and fibrinolysis (Fig 2) Before induction of labor there are changes in the coagulation system which may develop in cases of intrauterine death There are signs of hypercoagulability in the TEG such as shortening of the reaction time min) and a high maximal amplitud

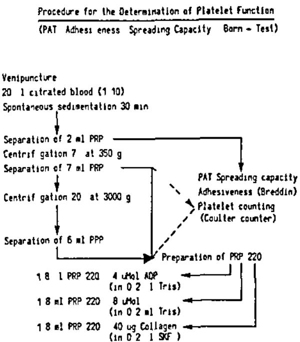


Fig 1 Procedure for the determination of platelet function

mm) the level of fibrinogen is quite high and the rate of formation of early FDP is increased which indicates the beginning of activation of fibrinolysis During treatment with oxytocin or PGF-α the level platelet count and TEG parameters unchanged The level of AT III however is in the three groups during application of it is constant during infusion of oxytocin in trast it decreases significantly suggesting consumption due to activation of thrombin

A remarkable increase of FDP during $PGF_{2}\alpha$ (i v and i a) and oxytocin infusion is found FDP values in these groups are significantly higher than in therapeutic abortion where they ranged from initially 0 4 μg/ml to a maximum of 5 3 μg/ml four hours after commencement In our opinion it is noteworthy to mention that in both groups oxytocin and $PGF_{2}\alpha$ liberation of material having fibrinolytic activity occurs to some extent This rate of release however is much lower than we found in cases of surgical curettage of a missed abortion (+ 1 250 per cent after the emptying of the uterus)

The initial values of plasminogen were of the same magnitude as those found in pregnant women and during treatment with both $PGF_{2}\alpha$ and oxytocin they remained unchanged

The activation of fibrinolysis however is also shown by the decreasing values of the inhibitor of fibrinolysis alpha 1 antitrypsin whereas alpha 2 macroglobulin remains unchanged

Platelet function Fig 3 demonstrates the effect of a single intraamniotic (i a) injection of 40 mg $PGF_{2}\alpha$ on ADP and collagen induced platelet aggregation and on spontaneous platelet aggregation

The parameters of aggregation show no significant differences neither in maximal aggregation nor in determining the angle of aggregation (speed of aggregation)

Parameters of disaggregation of clumped platelets expressed by disaggregation per cent and the angle of disaggregation were also unchanged after intraamniotic $PGF_{2}\alpha$

The investigations in the group receiving oxytocin infusions gave the following results (Fig 4) there is a significant increase of maximal aggregation by 8 μMol ADP and by collagen The speed of aggregation expressed by ctgα increases significantly after 4 and 8 μMol ADP The PAT shows no statistically significant differences The maximal disaggregation and the speed of disaggregation are slightly decreased These findings demonstrate a tendency for increased platelet aggregation during infusion of oxytocin in cases of missed abortion

The following changes in platelet functions were

		n	x̄	0	I	II	III
TEG r ( )	i						
ma (mm)	i v	9		12 9	12 5	12 4	11 7
		9		56 3	54 5	54 6	61 0
Fibrinoge (g %)	i	8		306		300	28
Platelets (x 1000)	i v	11		202	198	197	205
	i a	5		194	202	198	19
	O ytocin	8		284	283	288	
AT III (mg%)	i v	8		31 1	32 0	30 5	29 1
	i a	7		30 7	31 1	32 0	33 4
	O ytoci	8		31 6	29 3	27 1	
Plasminoge (g %)	i v	8		14 9	15 0	14 7	13 3
	i a	7		14 8	14 9	14 7	14 7
	O ytoci	8		17 3	16 6	16 7	
FDP (μg/ l)	i	10		8 8	14 0	16 5	10 5
	i a	6		4 6	13 9	24 2	25 0
	O ytocin	7		2 8	15 0	11 8	4 8
α_1AT (g%)	i v	8		384	362	396	378
	i a	7		294	295	302	333
	O ytoci	8		412	387	384	
α_2MG (g%)	i v	8		214	230	225	216
	i a	7		298	299	304	316
	O ytoci	8		235	228	233	

2 p < 0 05
< 0 01

Fig 2 Parameters of coagulation and fibrinolysis

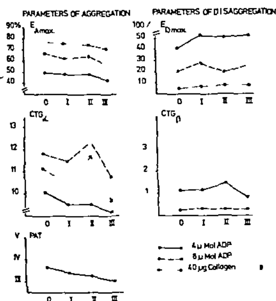


Fig 3 $PGF_{2}\alpha$ i a Platelet function

found during infusion of $PGF_{2}\alpha$ intravenously (Fig 5) The maximal aggregation is significantly reduced during infusion of $PGF_{2}\alpha$ The speed of aggregation also decreases significantly after one hour
Maximal disaggregation and also the speed of disaggregation increase significantly The overall effect on platelets is one of a decreased tendency to aggregate after infusion of $PGF_{2}\alpha$

This effect can also be demonstrated by the PAT Here we compared two groups missed abortion and therapeutic abortion The upper curve shows the remarkably increased initial value in the missed abortion group when compared with the therapeutic abortion group (lower graph) In both cases the degree of aggregation is reduced significantly

These results emphasize the effect of $PGF_{2}\alpha$ infusion on platelet function The inhibiting action of intravenous $PGF_{2}\alpha$ upon platelet aggregation means within the missed abortion group a reverting to normal of the increased tendency towards platelet aggregation

Interpretation and clinical conclusions There are many communications on hemostasis in cases of therapeutic abortion by $PGF_{2}\alpha$ (1 2 6 16) but not in association with intrauterine death Our investigations show that even in this high risk group there is no sign of intravascular consumption of the coagulation system during induction of labor by $PGF_{2}\alpha$ nor after emptying of the uterus

This finding might be explained by two factors

1) In contrast to the procedure of dilatation and curettage there is less mechanical trauma so the possibility of liberation of thromboplastic material may be reduced

2) Platelets which are known to be able to trigger off DIC (18) become less active during infusion of $PGF_{2}\alpha$ This altered platelet function which is constantly observed in vivo too may reduce or prevent the development of DIC and consumption of coagulation factors with consequent hemorrhage (7 8 11 20)

Similar features concerning the importance of platelet function are found in investigations concerning the role of platelet aggregates and platelet release reaction in initiating DIC in cases of bacterial shock (12)

The changes found in the fibrinolytic system associated with the use of $PGF_{2}\alpha$ or oxytocin in missed abortion are small when compared with those found with surgical evacuation of the uterus Nevertheless if the fibrin fibrinogen degradation products (FDP) are raised we should discuss whether one should use an inhibitor of fibrinolysis prophylactically (15)

Further studies will show whether or not it is possible to obtain additional protection against the development of changes in blood coagulation in cases of missed abortion and missed labor by a combination of antifibrinolytic agents and $PGF_{2}\alpha$

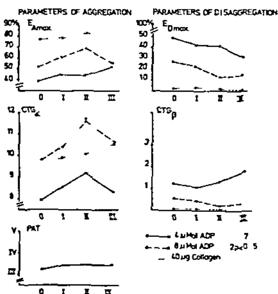


Fig 4 Oxytocin i v Platelet function

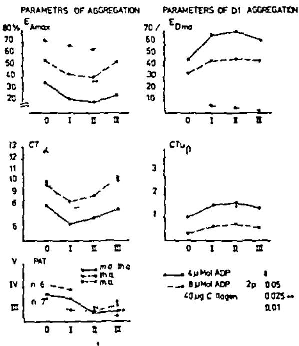


Fig 5 PGF$_2\alpha$ i v Platelet function

REFERENCES

1 Badraoui M H H Bonnar J Hillier K & Embrey M P Blood coagulation changes during midtrimester abortion induced by prostaglandin F₂α Brit med J *4 375* 1973

II W R & Wentz A C Abortion and coagulation rostaglandin JAMA Aug *27* 1082 1973

r F K Rosenberg M Kokker M & Douglas W Consumptive coagulopathy associated with ntra amniotic infusion of hypertonic salt Am J Obstet Gynecol *112* 534 1972

4 Born G K R Quantitative investigations into the aggregation of blood platelets *J Physiol 162* 67 1962

5 Breddin K Die Thromozytenfunktion bei haemorrhagischen Diathesen Thrombosen und Gefässkrankenheiten Thrombos Diathes haemorrh Suppl 27 1968

6 Brenner W E Fishburne J I McMillan C W Johnson A M & Hendricks C H Coagulation changes during abortion induced by prostaglandin $F_2\alpha$ Am J Obstet Gynecol *117* 1080 1973

7 Briel R C Kunz S Conradt A Unbehaun V Schlotter C M & Kidess E Labour induction by $PGF_2\alpha$ and its influence on platelet function International Conference on prostaglandins Florence May 26-30 1975

8 Cianci S Santangelo S Benjatto G & Reitano S The effect of induction of labour using PGF₂α on platelet aggregation International conference on prostaglandins Florence May 26-30 1975

9 Herschlein H J & Steichele D F Untersuchungen über das Auftreten von Fibrinogenspaltprodukten bei Patientinnen mit intrauterin abgestorbener Frucht und Defibrinierungssyndrom Med Welt *18* 3145 1967

10 Hickl E J Bandilla P & Kaether M Therapie mit Prostaglandin in der Gynäkologie Dtsch Med Wschr *99* 1566 1974

11 Irion E & Blomback H Prostaglandins in platelet aggregation Scand J Clin Lab Invest *24* 141 1969

12 Kuhn W & Graeff H Gerinnungsstörungen in der Geburtshilfe G Thieme Stgt 95 1970

13 Laros R K Collins J Penner J A Hage M L & Smith S Coagulation changes in Saline induced abortion Am J Obstet Gynecol *116* 277 1963

14 Pedersen P H Larsen J F & Soerensen B Induction of labour with PGF₂α in missed abortion Prostaglandins *2* 135 1972

15 Pfeifer G W Proteinasenblockade bei abgestorbener Schwangerschaft Dtsch Med Wschr 93 479 1968

16 Philips L L Mohajer Shojai E Dillon Th F Coagulation studies during second trimester abortions induced by $PGF_2\alpha$ Am J Obstet Gynecol *119* 577 1974

17 Reid D E Weimer A E Roby Ch L Diamond L K Maternal afibrinogenemia associated with long standing intrauterine fetal death Am J Obstet Gynecol *66* 500 1953

18 Rodriquez Erdmann F Intravascular activation of the clotting system with Phospholipids Production of the generalized Shwartzmann reaction with platelet factor 3 Blood *26* 541 1965

19 Sedaghat A Ayromloo J Disseminated intravascular coagulation resulting in severe hemorrhage following the intraamniotic injection of hypertonic saline to induce abortion Am J Obstet Gynecol *114* 841 1972

20 Sekhar M C Effect of eight prostaglandins on platelet aggregation J Med chem *13* 39 1970

21 Stauder R W Flessa H C Glueck H J Kisker C T Changes in maternal coagulation factors after intra amniotic injection of hypertonic saline Obstet Gynecol *37* 660 1971

Submitted for publication November 9 1977

R C Briel M D
Department of Obstetrics and Gynecology
Tübingen
West Germany

Acta Obstet Gynecol Scand 58 365–370 1979

ESTRADIOL ESTRIOL AND HUMAN PLACENTAL LACTOGEN IN SERUM IN THREATENED ABORTION

Jens B Hertz Jørgen Falck Larsen Birgit Svenstrup and Svend G Johnsen

From the Departments of Obstetrics and Gynecology Gentofte and Herlev Hospitals University of Copenhagen and the Hormone Department Statens Seruminstitut Copenhagen Denmark

Abstract In 64 pregnant women admitted to hospital because of threatened abortion the prognostic value of estradiol 17 beta estriol and human placental lactogen (HPL) in serum was examined The hormones were determined by radioimmunoassay Blood samples were taken at regular intervals during admission to hospital and subsequently until delivery For each hormone a reference range was based on the hormone values obtained from the pregnancies that continued to viability The study shows that the three hormones examined gave a good indication of the prognosis in threatened abortion both separately and in combination The best predictive values were achieved with estradiol and HPL after serial samples Of these two hormones estradiol is to be preferred because of its fetoplacental origin

Bleeding in early pregnancy is a frequent cause of admission to hospital At this early stage of pregnancy it is difficult on clinical grounds alone to determined whether the pregnancy will be doomed or may proceed to delivery It is of importance to recognize the failing pregnancies quickly so as to shorten a worrying and costly stay in hospital The prognostic value of several hormonal estimations have previously been investigated (2 3 4 5 6 12)

Human placental lactogen (HPL) reflects only placental function Fetoplacental function can be studied with estriol and has been used for this purpose in the second half of pregnancy In very early pregnancy estradiol is produced partly in the corpus luteum and partly in the placenta (11) Later in pregnancy estradiol is mainly synthesized in the placenta from both fetal and maternal precursors (1)

The purpose of the present study was to estimate the prognostic value of both single and serial samples of estradiol estriol and HPL separately and in combination

MATERIAL AND METHODS

Seventy two consecutive pregnant women admitted to the Department of Obstetrics and Gynecology Gentofte Hospital Copenhagen because of vaginal bleeding with or without lower abdominal pains from the 5th to the 20th weeks of pregnancy were studied Women included in the study fulfilled the following criteria

1) menstruation should have been regular with a well defined last period

2) the uterus was enlarged the cervix intact and the os closed

3) a positive pregnancy test was present

If spontaneous abortion occurred the products were examined histologically Eight patients were excluded Five because of treatment with progesterone one because of ectopic pregnancy one had a bleeding cervical polyp which could have caused the bleeding that brought the patient to hospital and one patient was evacuated because of low hormone levels and so did not abort spontaneously This left 64 patients in the final analysis

Blood samples for estradiol estriol and HPL determinations were taken shortly after admission daily for the first five days and then twice weekly while in hospital After discharge samples were taken at least once a month until end of pregnancy The blood samples were centrifuged and serum stored at 20 until assayed The results of the hormone determinations had no influence on the treatment of the individual patient

Serum unconjugated estradiol 17 beta was measured by radioimmunoassay using a specific antibody raised against 6-keto-estradiol coupled to bovine serum albumin via 6-o-(carboxymethyl)-oxime Ether extracts were chromatographed on a Sephadex LH 20 column equilibrated with benzene methanol (85 15 by vol) before radioimmunoassay The method of analysis only allowed estradiol to be determined up to 10 000 pg/ml (dilution was not performed) values which were reached in the 18th to 20th weeks of pregnancy The detection limit was 10 pg/ml

Serum unconjugated estriol was measured by radioimmunoassay without chromatography using a specific antibody raised against 6-keto-estriol coupled to bovine serum albumin via 6-o-(carboxymethyl)-oxime (8) Detection limit was 30 pg/ml

HPL was measured by radioimmunoassay Serum and



Fig 1 Age distribution in years at admission in patients with

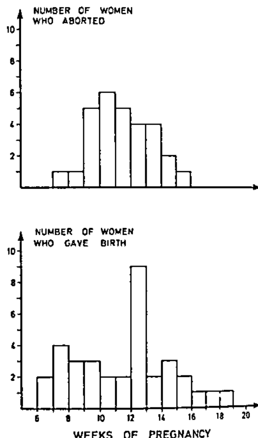


Fig 2 The gestational age at admission in patients with threatened abortion

... were mixed with isotopic labelled HPL and in ... with antibody Free and antibodybound HPL were separated with ammonium sulfate The standard was adjusted to 70/144 from Medical Research Council England Detection limit was 0 05 μg/ml

RESULTS

Of the 64 patients 29 (45 per cent) aborted and 35 (55 per cent) continued pregnancy until at least the 28th gestational week The age distribution at admission is presented on Fig 1 the gestational age at the time of admission on Fig 2 Patients who aborted were found to be significantly younger than patients who continued pregnancy (Mann Whitney rank sum test $p < 0\ 005$) Regarding the gestational age at the time of admission no significant difference was found between the two groups

The results of the estradiol estriol and HPL determinations are shown on Figs 3 4 and 5 respectively

A reference range was worked out for each analysis based on the hormone values obtained from the patients who continued pregnancy The values were presumed to be normally distributed when expressed logarithmically The equation expressing the increase during pregnancy was found and from that the 95 per cent reference range was determined (mean±two standard deviations) All the patients with unsuccessful outcome of the pregnancy are marked on the figures Single values are indicated with a filled circle When more than one determination was made in one patient the values are connected with solid lines Values from pregnancies proceeding to viability are only marked if any value from the first five days was below the lower limit of the reference range They are connected with broken lines In the following low vaules will refer to values below the lower limit of the reference range and normal values will mean values within the reference range

Estradiol (Fig 3) Low values were found in 24 of the 29 patients who aborted most of them showing

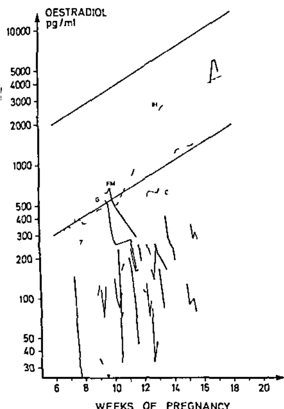


Fig 3 Estradiol in serum in threatened abortion
– Pregnancies proceeding to delivery — Pregnancies ending in abortion Single values from pregnancies ending in abortion
The 95 per cent reference range is indicated

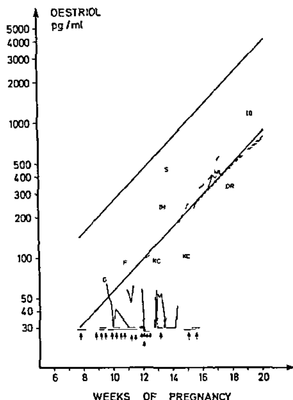


Fig 4 Estriol in serum in threatened abortion
-- Pregnancies proceeding to delivery — Pregnancies ending in abortion • Single values from pregnancies ending in abortion
The 95 per cent reference range is indicated

rapidly falling levels Of the remaining five patients three had normal values and two (FM GP) had initial values just above the lower limit of normal but subsequent values were increasingly below the reference range Two of the 35 patients who continued pregnancy until delivery had low values at the first sample but later values were higher and became normal

Estriol (Fig 4) Twenty four of the 29 patients with unsuccessful outcome had low values 18 of these showed undetectable levels of estriol (i e <30 pg/ml) One patient (GP) had normal levels of estriol at the first sample but later values were low Three patients (IO KC DR) who continued pregnancy until delivery had low values at the first blood sample suggesting an unfavorable outcome of the pregnancy In two of these the following values increased to normal levels In the third (KC) the next two values fell to levels below the detection limit before rising ultimately to the lower end of the normal range

HPL (Fig 5) Twenty four of the patients who aborted had low values 11 of these had undectable levels of HPL (i e <0 05 μg/ml) One patient (EK) showed normal levels of HPL at the first sample but *after two days values were low In three successful* pregnancies the first vales were low predicting unsuc

Table I *The predictive values for estradiol in serum in threatened abortion*

	First sample		Serial samples	
	Pat s who aborted	Pat s who gave birth	Pat s who aborted	Pat s who gave birth
Low values	24	2	26	0
Normal values	5	33	3	35

Predictive value of a positive test *first sample* 24/26 = 92%, *in serial samples* 26/26 = 100%

Predictive value of a negative test *in first sample* 33/38 = 87% *in serial samples* 35/38 = 9 %

3 Genazzani A R Cocola F Neri P & Fioretti P Human chorionic somatomammotropin (HCS) plasma levels in normal and pathological pregnancies and their correlation with the placental function Acta Endocrinol (Kbh) Suppl 167 1972
4 Kunz J & Keller J P HCG HPL oestradiol progesterone and AFP in serum in patients with threatened abortion Br J Obstet Gynaecol *83* 640 1976
5 Niven P A R Landon J & Chard T Placental lactogen levels as guide to outcome of threatened abortion Br Med J *3* 799 1972
6 Nygren K G Johansson E D B & Wide L Evaluation of the prognosis of threatened abortion from the peripheral plasma levels of progesterone estradiol and human chorionic gonadotropin Am J Obstet Gynecol *116* 916 1973
7 Pavlou C Chard T & Letchworth A T Circulating levels of human chorionic somatomammotropin in late pregnancy Disappearance from the circulation after delivery variation during labour and circadian variation J Obstet Gynaecol Br Comm *79* 629 1972
8 Svenstrup B Radioimmunologisk bestemmelse af frit østriol i serum under graviditet Ugeskr Laeger *138* 1075 1976
9 Tulchinsky D & Abraham G E Radioimmunoassay of plasma estriol J Clin Endocrinol Metab *33* 775 1971
10 Tulchinsky D & Korenman S G The plasma estradiol as an index of fetoplacental function J Clin Invest *50* 1490 1971
11 Tulchinsky D & Hobel C J Plasma human chorionic gonadotropin estrone estradiol estriol progesterone and 17 alpha hydroxyprogesterone in human pregnancy Am J Obstet Gynecol *117* 884 1973
12 Ylikorkala O & Jouppila P Human placental lactogen (HPL) in serum in complicated early pregnancy J Obstet Gynaecol Br Comm *80* 1040 1973

Submitted for publication February 1 1978

Jens B Hertz M D
Kirsten Piils vej 10
DK 2920 Charlottenlund
Denmark

Acta Obstet Gynecol Scand 58 371 – 373 1979

THE EFFECT OF MISSED ABORTION AND SPONTANEOUS ABORTION ON THE FATE OF SUBSEQUENT PREGNANCIES

S Levin E Amsterdam I Brook V Insler

From the Department of Obstetrics and Gynecology Government Hospital Donolo-Zahalon Tel Aviv Jaffa and Tel Aviv University Sackler Medical School Israel

Abstract Sixtytwo patients with spontaneous abortion and 58 with missed abortion were all promptly treated with curettage The reproductive performance and the subsequent fertility of both groups during a five year period before and after the abotion were compared To our surprise no significant differences were found between the two groups

Missed abortion (M A) is usually defined as a delayed expulsion of a pregnancy that ceased to develop It is customary to consider missed abortion as an entity different from spontaneous abortion (S A) particularly with regard to complications such as blood coagulation defects and also with regard to the future fertility of the patient To our surprise a thorough search of pertinent literature of the last ten years did not reveal even a single article dealing with the reproductive performance of women who have had a missed abortion We did find a few publications regarding the fate of pregnancies following induced abortion and spontaneous abortion (Pantelakis 1973 Papaevangelou 1973 Oelsner 1974)

The aim of the present study was to investigate and compare the effect of missed abortion and spontaneous abortion on the reproductive performance of women

MATERIAL AND METHODS

Medical files of patients treated in the department of obstetrics and gynecology Government Hospital Zahalon in Tel Aviv during the year 1971 were reviewed One hundred and fifty patients who underwent a curettage because of missed abortion and 150 women treated for spontaneous abortion during the same period were contacted by mail and invited to participate in this study Some women could not be contacted because of change of address change of name etc some were unwilling to participate because of personal reasons some patients had to be excluded because of medical reasons (incomplete case history folders etc) or because of family reasons (divorce)

Missed abortion was diagnosed when the difference between the expected and actual uterine size exceeded four weeks of pregnancy when immunological pregnancy test was negative and when no active uterine bleeding was present All patients with spontaneous abortion presented with significant uterine bleeding and usually with some degree of dilatation of the cervix The group of spontaneous abortion included 47 pregnancies of less than 12 weeks and 15 late incomplete abortions (13 24 weeks)

Patients of either group with uterine size not exceeding 12 weeks were treated by dilatation and curettage In patients with uterine size exceeding 12 weeks the curettage was usually preceded by oxytocin infusion

Broad spectrum antibiotics had been prophylactically administered to all patients for a five day period following curettage

Complications such as hemorrhage or infection had not occurred in either of the groups

The average duration of hospitalization for patients of both groups was 1 2 days

At the interviews carried out in 1976/77 medical and gynecological history of each patient prior to the abortion in 1971 was verified and a detailed medical and fertility history covering the five year period following the abortion was obtained

Among the 58 patients with missed abortion three had gestational diabetes two had hyperthyroidism and one patient delivered twice a baby with congenital atresia of esophagus prior to the missed abortion in 1971

Among the 62 patients with a spontaneous abortion there was one case of hyperthyroidism and one case of hypertension In none of the 120 couples was there evidence of blood

Table 1 *Age of patients with missed abortions and spontaneous abortions*

Maternal age	No of patients with missed abortions	No of patients with spont abortions
20 – 24	16	13
25 – 29	13	16
30 – 34	16	12
35 – 39	11	15
40 – 45	2	6
Total	58	62

Table II *Total number of pregnancies and mode of termination prior to the abortion*

Group	Missed abortion[a] No	%	Spontaneous abortion[b] No	%
Partus spontaneous	114	78 1	118	73 8
Stillbirths	2		3	
Caesarean section	4	2 7	2	1 3
Missed abortion	8	5 4	3	1 9
Spontaneous abortion	20	13 8	37	23 0
Live children	116	79 5	117	73 1
Sterility	1		0	
Average birth weight	3350		3150	
Number of premature infants (>2500 g)	8		6	
Induced abortion	18		12	
Total pregnancies	146†		160†	

[a] 58 women [b] 62 women

relation between wife and husband None of the patients interviewed reported the occurrence of chronic or systemic disease during the five years period between the curettage and the interview In 14 women a hysterosalpingoraphia was made following treatment of missed abortion and in none were intrauterine adhesions found In two patients the hysterogram revealed internal cervical os incompetence and a cervical suture (Macdonald method) was performed in both these patients in their following pregnancies

The reproductive performance of the patients before and after missed and spontaneous abortion respectively was compared

The total number of pregnancies and their mode of ter ion during a five year period before and after the were also compared

lude possible influence of age on fertility the same was performed once more on patients who at ime of abortion *in 1971 were less than 35 years old and* who desired children during the five years follow up There were 41 such patients in the missed abortion group and 37 in the spontaneous abortion group

In calculation of percentages induced abortions were excluded since it was impossible to establish how these pregnancies would terminate if allowed to continue

The statistical evaluation of the results was performed using the χ_2 (chi square) test

RESULTS AND DISCUSSION

The past reproductive performance of the 58 patients with missed abortion and of the 62 women who underwent a curettage for spontaneous abortion is summarised in table II No differences between the two groups were observed except for the fact that patients with missed abortion had in the past more induced abortions (*18* and *12* respectively) and more missed abortions (8 and 3 respectively) as compared to their counterparts with spontaneous abortion

Table III *Total number of pregnancies and their mode of termination during the 5 years period before the abortion as compared to a 5 years period after the abortion*

Group	Missed abortion Before No	%	After No	%	Spontaneous abortion Before No	%	After No	%
Partus spontaneous	56	74 6	59	67 0	59	75 6	48	65 7
Stillbirths	3		4		3		0	
Caesarean section	1	1 4	7	8 0	1	1 3	4	5.5
Missed abortion	3	4 0	5	5 7	1	1 3	0	0
Spontaneous abortion	15	20 0	17	19 3	17	21 8	21	28 8
Live children	54	72 0	62	70 5	57	73 0	52	71 2
Sterility	1		5		0		11	
Average birth weight	3300		3250		3100		3150	
Number of premature infants (>2500 g)	4		6		3		2	
Induced abortion	13		5		8		15	
Total pregnancies†	75		88		78		73	

† Pregnancies terminated by induced abortion not included

The reproductive performance of women during a period of five years before and a period of five years following missed abortion was not significantly different ($p>0\ 1$) In the group of 58 women there were 75 pregnancies resulting in *54 living children before* the missed abortion and 88 pregnancies resulting in 62 living infants following the missed abortion

The incidence of abortion (spontaneous and missed) was very similar during the two 5 years periods *In the five year period following* missed abortion there were more cesarean sections (seven as compared to one) and an increased incidence of sterility problems (five patients compared to one) The incidence of premature babies was slightly but not significantly increased (table III)

When the reproductive performance of women who underwent missed abortion was compared to that of patients who underwent spontaneous abortion no significant differences in the number of pregnancies and their mode of termination were revealed (table III)

In order to obtain even more objective data the same comparision of reproductive performance was

Table IV *Comparison of patients who at time of abortion were less than 35 years old and during 5 years follow up desired children*

Group	Missed abortions[a] No	%	Spontaneous abortions[b] No	%
Partus spontaneous	51	74 0	43	70 5
Stillbirths	4		0	
Caesarean section	5	7 2	3	4 9
Missed abortion	2	2 9	0	0
Spontaneous abortion	11	15 9	15	24 6
Live children	52	75 4	46	75 4
Sterility	5		7	
Average birth weight	3220		3130	
Number of premature infants (>2500 g)	5		2	
Induced abortion	5		11	
Total pregnancies	69†		61†	

[a] 41 cases [b] 37 women
† Pregnancies terminated by induced abortion not included

carried out on the two groups of patients (following missed abortion and spontaneous abortion) after exclusion of women at the time of curettage in 1971 were more than 35 years old or did not desire children during the five years follow up period (table IV) Again the differences between the incidence of pregnancies and mode of their termination were not statistically significant On the contrary patients who underwent missed abortion delivered 52 living infants (75 4 per cent) and had less spontaneous abortions (15 9 per cent) as compared to patients who underwent curettage because of spontaneous abortion (75 4 per cent of living children and 24 6 per cent of spontaneous abortion)

The incidence of sterility was similar in both groups (five women in the missed abortion group and seven patients in the spontaneous abortion group)

The incidence of prematurity was somewhat higher in the missed abortion group

Analysis of the above data permits the conclusion that the future fertility and the reproductive performance (as judged by the incidence of pregnancies producing a live baby) are not significantly different in women who underwent a missed abortion as compared to women who had a simple spontaneous abortion (table II IV)

This result is somewhat surprising since many gynecologists believe that missed abortion is an entity totally different from a straightforward spontaneous abortion so far as possible complications morbidity and future fertility are concerned (Borglin 1957)

The treatment study revealed that missed abortion and its treatment does not significantly impede future reproductive performance of women

REFERENCES

1 Borglin N G Missed Abortion Analysis of 10 Year Series Acta Obstet Gynecol Scand *36* 512 1957
2 Oelsner G David A Insler V & Serr D M Outcome of Pregnancy after treatment of intrauterine adhesions J Obstetrics and Gynecology *44* 341 1974
3 Pantelakis S N Papadimitriou G C & Doxiadies S A Influence of induced and spontaneous abortions on the outcome of subsequent pregnancies Am J Obstet Gynecol *116* 799 1973
4 Papaevangelou G Vrettos A S Papadatos C & Alexiou D The effect of spontaneous and induced abortions on prematurity and birthweight J Obstet Gynec Brit Cwlth *80* 418 1973

Submitted for publication November 14 1977

Samuel Levin M D
Department of Obstetrics and Gynecology
Government Hospital Donolo-Zahalon
Tel Aviv Jaffa
Israel

Acta Obstet Gynecol Scand 58 375–378 1979

BROMOCRIPTINE TREATMENT OF THE PREMENSTRUAL SYNDROME

Stig Kullander and Lars Svanberg

From the Department of Obstetrics and Gynecology at the University of Lund Malmö General Hospital Malmö Sweden

Abstract Bromocriptine 2 5 mg twice a day was tested for its effect on premenstrual tension in a random double blind cross-over trial

1 The compound tended to lessen the symptoms especially mastodynia

2 Serum prolactin levels around the upper limit of the normal range were significantly lowered Patients with the highest starting prolactin levels had the most severe symptoms and in these patients the fall in the levels was greatest

3 Serum FSH and LH levels were significantly reciprocally influenced compared with serum prolactin Serum estradiol 17 beta and progesterone did not change during treatment

4 The bromocriptine treated cycles were all ovulatory according to basal temperature levels The luteal phase was prolonged when serum FSH was raised

The premenstrual syndrome is a complex of disorders during the second half of the menstrual cycle which disappears when the actual menstrual flow commences The clinical picture usually includes mastodynia gain in weight and psychic symptoms such as headache nervous tension and tendency to depression Treatment of this syndrome has hitherto been non specific and symptomatic and consisted of diuretics tranquillizers or progesterone Because of the effects of prolactin on the fluid and electrolyte balance Horrobin (12) and Cole *et al* (6) suggested that this hormone might play an important role in the etiology of the syndrome With this possibility in mind they studied bromocriptine a long acting dopaminergic agonist for its clinical effect on a case of premenstrual tension with affective disorders The effect was good Dopamine is probably the physiological prolactin inhibiting factor (3) Benedek Jaszmann *et al* (4 5) found bromocriptine in a dose of 2 5 mg twice a day significantly alleviated the mental symptoms mastodynia and edema in 10 women with premenstrual complaints while a placebo produced no improvement However the prolactin levels in these cases though lowered by the bromocriptine never exceeded the upper normal limits The isolated symptom of premenstrual mastodynia has also sometimes been successfully treated with bromocriptine in a dose of 5 mg per day (19)

In that study plasma progesterone levels measured prior to treatment during the follicular phase were normal Mitigation of premenstrual mastodynia after bromocriptine treatment of normoprolactinemic women has also been reported by Anderson *et al* (1)

Halbreich *et al* (10) however found that 28 women with the premenstrual syndrome had a significantly higher serum prolactin level throughout the menstrual cycle than a control group as well as a steeper increase during the premenstrual period Bromocriptine may have other actions that are independent of the suppression of prolactin release as has been recently shown in cases of normoprolactinemic amenorrhea in which plasma 17 beta-estradiol increased and menstruation returned (20)

The purpose of our investigation was to demonstrate any connection between the occurrence of premenstrual symptoms and disturbed prolactin levels and to find out whether bromocriptine is useful in the treatment of the syndrome

MATERIAL AND METHODS

The clinical material consisted of 10 women aged 27 to 46 (mean 37 5) All had premenstrual symptoms such as mastodynia gain in weight depression edema and head ache Each symptom was assessed and allotted a score of 0 to 3 first during the control cycles (Table I)

In a double blind cross over trial the patients were given at random for two consecutive cycles bromocriptine or placebo tablets of identical appearance Each woman served as her own control From the 14th day until menstruation in each cycle the women took oral tablets (2 5 mg) twice a day after meals The patients returned to the hospital just after the outset of the menstrual flow and their premenstrual symptoms were assessed again Basal body temperature recordings were made throughout all the cycles

The plasma prolactin levels were determined during the luteal phase (21 22nd cycle day) at the same time in the morning in all patients (13) In 7 of the patients plasma follicle stimulating hormone (F S H) luteinizing hormone (LH) estradiol and progesterone were estimated by radioimmunoassay (8 14 22 23) The assays were made in duplicate and the means were used

Statistical methods Standard procedures were used The significances of differences between the observation were calculated with Student s t test

Table I *Premenstrual symptoms during control cycle in 10 patients*

	Cycle before treatment
Mastodynia	
number	9
mean score	2 1
Gain in weight (obj weighed >0 5 kg)	
number	10
mean score	1 1
Depression	
number	6
mean score	2 3
Edema (subj hands and feet)	
number	5
mean score	1 2
Headache	
number	4
mean score	1 4

Score 0=none 1=mild 2=moderate 3=severe

Table II *Effect of treatment of main premenstrual symptoms*

	Cycle before treatment	Cycle with bromocriptine	Cycle with placebo
Mastodynia			
number	9	9	9
mean score	2 1	0 6	1 9
therapeutic effect		6	3
Gain in weight			
number	10	10	10
mean score	1 1	0 5	0 9
therapeutic effect		4	2
Depression			
number	6	6	6
mean score	2 3	1 6	1 2
therapeutic effect		2	4

Score 0=none 1=mild 2=moderate 3=severe

RESULTS

All premenstrual symptoms were decreased during both placebo and bromocriptine treatment Mastodynia *improved most during the treatment with* bromocriptine but the improvement was not statistically proved (Table II) Examination of the breasts showed no abnormalities such as galactorrhea and no changes during treatment with bromocriptine or of placebo

The study showed a significant effect of bromo on the prolactin levels During the placebo prolactin level bordered or slightly exceeded upper limit (3 15 ng/ml) but during treat with bromocriptine the prolactin level was significantly suppressed (Fig 1 and Table III) The patients with the highest scores for the premenstrual symptoms had the highest prolactin levels in the study (Fig 2) and the greatest falls during treatment with bromocriptine During the use of bromocriptine the prolactin level tended to be constantly about 5 ng/ml

Seven patients had side effects such as nausea and dizziness for a couple of days but all continued the trial Only 3 of the 10 patients had *no such side effects* and 2 patients reported minor nausea during the placebo period

It was noteworthy that the serum FSH and LH were increased during the treatment with bromocriptine ($p<0\ 05$) Estradiol and progesterone levels however showed no differences and were all within the normal ranges (Table III)

Ovulation was confirmed by basal body temperature recordings in all placebo as well as bromocriptine cycles There was no significant difference in the absolute mean length of the luteal phase but in 6 of the fully investigated women the luteal phase was prolonged during the bromocriptine cycle In each of these 6 cases the serum FSH also was increased in the *same cycle In the seventh woman* FSH was lowered and the luteal phase shorter

DISCUSSION

Plasma prolactin levels tended to be at the upper end of the normal range during the placebo cycle and showed a positive correlation with the symptom

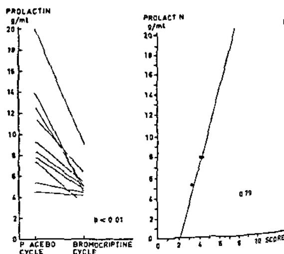


Fig 1 Prolactin levels during placebo and bromocriptine cycle

Fig 2 The relation between premenstrual symptoms (according to score number) and prolactin levels

Table III *Effects of bromocriptine on serum prolactin FSH LH estradiol and progesterone in luteal phase*

Patient no	normal range	Prolactin ng/ml (2 15)	FSH µg/l (0 5 3 0)	LH µg/l (0 5 3 0)	E_2 pg/ml (80-290)	Progesterone ng/ml (2 5 13 0)
1	placebo	4 5	1 9	1 1	175	10 0
	bromocriptine	4 2	2 9	2 6	148	9 6
2	placebo	20 0	1 1	1 1	240	17 0
	bromocriptine	9 1	2 9	2 8	193	2 7
3	placebo	5 3	2 1	1 5	142	9 2
	bromocriptine	4 5	2 0	1 9	140	4 4
4	placebo	11 3	1 3	2 4	122	7 0
	bromocriptine	6 4	1 8	1 7	130	16 1
5	placebo	9 3	1 6	1 2	170	4 9
	bromocriptine	5 5	2 3	1 4	298	12 0
6	placebo	8 3	4 2	1 6	160	13 0
	bromocriptine	5 1	4 2	3.2	202	16 7
7	placebo	7 7	4 6	2 6	335	3 6
	bromocriptine	3 5	5 4	3 4	93	9 5
8	placebo	7 7				
	bromocriptine	4 9				
9	placebo	14 0				
	bromocriptine	4 7				
10	placebo	12 5				
	bromocriptine	5 0				

score Treatment with bromocriptine lowered the prolactin levels but did not affect the symptom scores significantly although the values tended to show improvement especially in mastodynia This suggests that prolactin is involved in the premenstrual syndrome

It has been shown that bromocriptine can relieve premenstrual tension (6) However Ghose and Coppen (9) found a dose of 2 5 mg a day to have no such effect in 13 patients with premenstrual tension In none of these investigations was the plasma prolactin level above the upper limit of the normal range Perhaps the symptoms are due to an increased sensitivity to prolactin in association with an increased number of prolactin receptors In our relatively small group bromocriptine tended to improve mastodynia and weight gain but did not affect depression

One of the targets of prolactin is the kidneys with consequent retention of water potassium and sodium (11) Consequently the inhibition of prolactin by bromocriptine should stimulate the excretion of electrolytes and cause diuresis (17) thereby having a favorable effect on edema and on engorged and painful breasts

Opinions differ on the role of prolactin in the mechanism of ovulation and corpora lutea function and its variation during the menstrual cycle Robyn *et al* (18) found that the serum prolactin level rises during the follicular phase to reach a peak at mid-cycle just before ovulation and that the level is high also in the luteal phase These changes were accompanied by parallel changes in the estrogen levels in the blood However other investigators (15) have not found any significant variation of the prolactin level during the menstrual cycle Such variation if any does not seem to be necessary for normal gonadal function since our patients with suppressed prolactin ovulated and had normal estrogen and progesterone levels

A reciprocal relation has been assumed between the hypothalamic pituitary mechanisms controlling the secretion of gonadotrophin and prolactin i e an increase in either of these hormones is accompanied by a decrease in the other This assumption is mainly based on experiments in rats (2)

Pepperell *et al* (16) found that the serum FSH and the LH rose during treatment with bromocriptine but only if the prolactin levels were high already before treatment In 10 women with premenstrual tension Benedek Jaszman *et al* (5) found bromocriptine increased the concentration of LH in the blood suppressed prolactin but had no effect on the level of FSH or estradiol Our investigation showed increase in both FSH and LH during treatment with bromocriptine and the patients continued to have regular

ovulatory menstruations Their tendency to a pro longed luteal phase might be explained by the increas ed FSH stimulating more rapid follicular growth

The release of prolactin from the pituitary is in hibited from the hypothalamus by a prolactin in hibiting factor believed to be dopamine (21) Bromocriptine a synthetic secale alkaloid of peptide type acts like a dopamine agonist with a prolactin in hibiting effect Experimental studies suggest that bromocriptine also has a direct inhibitory effect on the prolactin secreting cells in the pituitary and on higher centers (7)

Judging from cumulative evidence and from our experiments bromocriptine is valuable in the treat ment of premenstrual complaints especially masto- dynia and edema

REFERENCES

1 Andersen A N Larsen J F Steenstrup O R Svendstrup B & Nielsen J Effect of bromocriptine on the premenstrual syndrome A double blind clinical trial Brit J Obstet Gynaec *84* 370 1977

2 Ben David M Danon A & Sulman F G Evidence of antagonism between prolactin and gonadotrophin secretion Effect of methallibure on perphenazine induced prolactin secretion in ovariectomised rats J Endocrinology *51* 719 1971

3 Benedek Jaszmann L J & Sternthal W Advances in the treatment of the galactorrhoea amneorrhoea syndrome Induction of ovulation and inhibition of lacta with 2 bromo alpha-ergocryptin Geburtsh lk *34* 59 1974

aszmann L J Lequin R M & Sternthal Treatment of the premenstrual syndrome with bromocriptine Acta Endocr Suppl *193* 29 1975

5 Benedek Jaszmann L J & Hearn Sturtevant M D Premenstrual tension and functional infertility Aetiology and treatment Lancet I 1095 1098 1976

6 Cole E N Evered D Horrobin D F Manku M S Mtabaji J P & Nassar B A Is prolactin a fluid and electrolyte regulating hormone in man? J Physiol *252* 54 1975

7 Del Pozo E & Flückiger E In Human prolactin Ed J L Pasteck and C Robyn Amsterdam 1973

8 Edquist L E & Johansson E D B Radioimmunoassay of oestrone and oestradiol in human and bovine peripheral plasma Acta Endocr (Kbh) *71* 716 1972

9 Ghose K & Coppen A Bromocriptine and premenstrual syndrome controlled study Brit Med J *1* 147 1977

10 Halbreich K Assael M Ben David M & Boenstein R Serumprolactin in women with premenstrual syndrome Lancet II 654 1976

11 Horrobin D F Lloyd I J Lipton A Barstyn P S Durhin N & Muiruri K L Actions of prolactin on human renal function Lancet *2* 352 1971

12 Horrobin J F Prolactin Medical and Technical Publ Co Ltd Lancaster 1973

13 Hwang P Guyda H & Friesen H A radioimmunoassay for human prolactin Proc Nat Acad Sci USA *68* 1902 1971

14 Lindberg B S Lindberg P Martinsson K & Johansson E D B Radioimmunological methods for the estimation of oestrone oestradiol 17 beta and oestriol in pregnancy plasma Acta Obstet Gynecol Scand Suppl 32 1974

15 McNeilly A S & Chard T Circulating levels of prolactin during the menstrual cycle Clin Endocrinol *3* 105 1974

16 Pepperell R J Evans J H Brown J B Bright M J & Smith M I A study of the effects of bromocriptine on serum prolactin follicle stimulating hormone and luteinizing hormone and on ovarian responsiveness to exogenous gonadotrophins in anovulatory women Brit J of Obst & Gynaec *84* 456 1977

17 Richardsson B P Evidence for a physiological role of prolactin in osmoregulation in the rat after its inhibition by 2 bromo-α-ergocryptine Brit J Pharmacol *47* 623 1973

18 Robyn C Delooye P Nohin J Vehemans M Badawi M Pesez Lopez F R & L Hermite M *In* Proceedings of the International Symposium on Human Prolactin Brussels 1973 Excerpta Medica Foundation p 167 Amsterdam 1973

19 Schulz K D Del Pozo E Lose K H Künzig H J & Geiger W Successful treatment of mastodynia with the prolactin inhibitor bromocryptine (CB 154) A. h Gynäk *220* 83 1975

20 Seppälä M Hirvonen E & Ranta T Bromocriptine treatment of secondary amenorrhoea Lancet I 1154 1156 1976

21 Takahara J Arimura A & Schally A V Effect of catecholamines on the TRH stimulated release of prolactin and growth hormone from sheep pituitaries in vitro Endocrinology *95* 1490 1974

22 Thorell J I & Holmström B Production of antisera against highly purified human follicle stimulated hormone luteinizing hormone and thyroid stimulating hormone J Endocr *70* 335 1976

23 Thorneycroft I H & Stone S C Radioimmunoassay of serum progesterone in women receiving oral contraceptive steroids Contraception *5* 129 1972

Submitted for publication March 14 1978

Stig Kullander M D
Department of Obstetrics and Gynecology
Malmö General Hospital
S 214 01 Malmö
Sweden

Acta Obstet Gynecol Scand 58 379–383 1979

TREATMENT OF HYPERPROLACTINEMIC LUTEAL INSUFFICIENCY WITH BROMOCRIPTINE

A N Andersen J F Larsen P C Eskildsen M Knoth S Micic B Svenstrup and J Nielsen

From the University Department of Obstetrics and Gynecology the Department of Internal Medicine and Endocrinology Herlev Hospital the University Department of Pathology Hvidovre Hospital and the Hormone Department Statens Serum Institut Copenhagen Denmark

Abstract Twelve patients with infertility and insufficient luteal function were studied during a control cycle and during a cycle when 2 5 mg of bromocriptine was given twice daily Serum levels of prolactin progesterone estradiol 17 β FSH and LH were determined during both cycles Endometrial biopsies were taken from most patients during the late luteal phase

Two patients had persistent hyperprolactinemia approximately 35-45 ng/ml and both had repeated insufficient luteal function which completely reverted to normal during treatment Five of the 10 normoprolactinemic patients achieved a normal luteal function during bromocriptine therapy No pregnancies were achieved during the study but one patient later conceived during bromocriptine therapy

Increased prolactin secretion as found in hyperprolactinemic amenorrhea may impair ovarian steroid secretion (2 12) The pathological role of abnormal prolactin secretion in women with preserved menstrual period is however still not documented although some studies indicate an association between hyperprolactinemia and luteal insufficiency (1 5) An in vitro study (7) using human granulosa cells indicates that a certain amount of prolactin is essential for normal ovarian steroid secretion while increased levels might have a direct suppressive effect on ovarian progesterone synthesis It is the aim of the present study to assess the influence of prolactin and the effect of treatment with bromocriptin in patients with abnormal luteal function

PATIENTS AND METHODS

The study comprised 12 patients between 26 and 35 years of age all with known luteal insufficiency and infertility

(Patient HFr used mechanical contraception and was *not* attending the infertility clinic but had her hormone profile investigated because of symptoms of severe premenstrual syndrome)

Prolactin levels and luteal phase characteristics during a control and bromocriptine cycle in 12 patients with abnormal luteal function

	Control cycle					Bromocriptine cycle			
Patients	Duration of cycle (days)	Prolactin follicular phase	Prolactin luteal phase	Progesterone luteal phase	Endometrial biopsy	Duration of cycle (days)	Prolactin (mean)	Progesterone luteal phase	Endometrial biopsy
HF	44	45 0	44 2	LI		25	5 7	NOR	
AS	46	33 5	35 6	LI	LI	33	6 3	NOR	NOR
ZG	32	13 7	10 5	LI		44	3 7	NOR	
HFr	27	9 6	14 2	LI		26	5 1	NOR	
KD	46	7 1	6 6	LI	LI	31	3 5	LI	LI
GLN	33	11 8	9 6	LI	LI	27	5 0	LI	LI
LB	22	6 4	16 2	LI	LI	23	7 1	LI	
JF	24	8 8	15 0	NOR	LI	26	5 3	NOR	LI
BD	28	6 0	5 3	NOR	LI				
LG	28	9 5	10 6	NOR	LI	27	6 1	NOR	NOR
IHO	30		10 9	NOR	LI	25		NOR	NOR
MR	27	5 0	11 0	NOR	LI	26	4 7	NOR	NOR

1) LI means luteal insufficiency defined as peak serum progesterone below 10 ng/ml NOR means normal

2) LI means luteal insufficiency defined as more than two days delay in the endometrial development NOR means normal

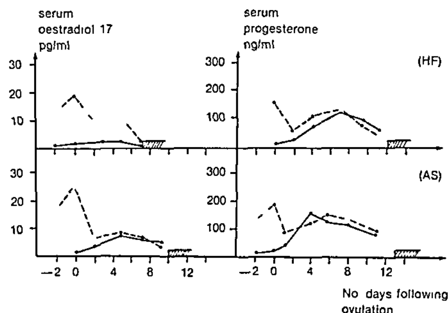


Fig 1 Luteal phase serum concentrations of progesterone and estradiol 17-β during control and bromocriptine cycles in two hyperprolactinemic patients
--- estradiol 17-β
— progesterone

The diagnosis of luteal insufficiency was based on a luteal phase of 12 days or less a peak serum progesterone level of less than 10 ng/ml during the luteal phase and/or an endometrial biopsy revealing a delay in the development of the endometrial histology of more than two days

Three patients (HF AS and KD) had cycles ranging between 35 and 65 days All others had a fairly regular cycle 28 days None of the patients had galactorrhea ex who had a profuse galactorrhea following the pre of oral contraceptives

The trial initially included a control cycle ut any medication followed by a treatment cycle iere 2 5 mg of bromocriptine (Parlodel[R]) was given twice daily during the whole cycle During both cycles the following recordings were made

a basal body temperature

b basal serum levels of FSH LH progeserone and estradiol 17 β were determined on the 10th day of the cycle and on every second day during the luteal phase

c serum prolactin at least once during the follicular and luteal phases

d an endometrial biopsy from most patients during the late luteal phase

Assay methods Serum estradiol 17 β was determined by a radioimmunoassay using a specific antibody to 6-keto-estradiol which was bound to bovine serum albumin via 6-0 (carboxymethyl) oxime and separation was performed on a sephadex LH 20 column Progesterone was extracted with petroleum ether and estimated by radioimmunoassay using antibody to 11 OH progesterone bound to bovine serum albumin Serum FSH and LH were measured by a specific double antibody radioimmunoassay (8 9) The human pituitary preparation LER 907 (NIH) was used as standard in both assays Serum prolactin was determined by a double antibody radioimmunoassay using reagents supplied by the National Pituitary Agency Purified human prolactin was labelled with ^{125}I by the chloramine T method and donkey antirabbit gamma globulin (Wellcome) was used as second antibody The sensitivity limit of the assay was 2 5 ng/ml the interassay variation 8 0 per cent and the intraassay variation 5 5 per cent The basal levels in normal women are 9 1±2 2 ng/ml (mean±SD) Range 3 0 to 13 5 ng/ml Hormone levels in the two cycles were compared statistically using t test on paired observations

RESULTS

Results are summarised in Table I

Two patients (HF and AS) had hyperprolactinemia with serum prolactin levels about 35-45 ng/ml One had galactorrhea and both had luteal insufficiency during the control cycle Bromocriptine therapy completely converted the lutal phase steroid secretion to normal (Fig 1) as well as the duration of the cycle and the lutal phase During therapy an increase was found in the follicular phase FSH and LH (below 4 IU/ml) Increments during the luteal phase were more pronounced (FSH approximately 5 IU/ml and LH approximately 11 IU/ml)

As seen in Table I all other patients had normal mean levels of prolactin although three had single samples with slightly elevated values Five of the normoprolactinemic patients (ZG HFr KD GLN and LB) were found to have subnormal peak proges

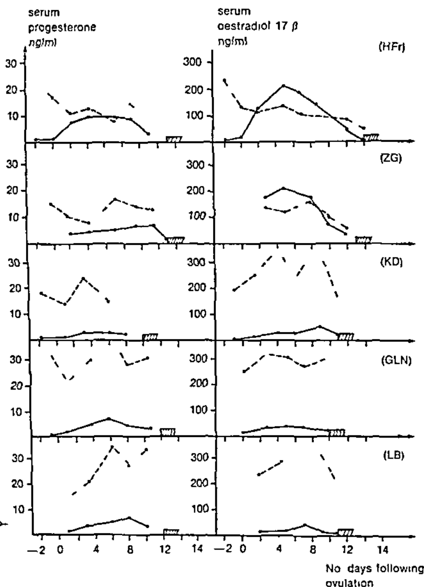


Fig 2 Luteal phase serum concentrations of progesterone and estradiol 17 β during control and bromocriptine cycles in five normoprolactinemic patients with hormonal signs of luteal insufficiency
-- estradiol 17 β
— progesterone

terone concentrations during the control cycle (Fig 2) Bromocriptine medication converted the luteal phase steroid secretion to normal in two patients (ZG and HFr) but had no effect in the remaining three (Fig 2) The medication did not cause any persistent change in FSH or LH concentrations irrespective of whether the patient responded to treatment or not

With the exclusion of the two patients with true hyperprolactinemia (HF and AS) the serum prolactin concentration was 8 7±2 4 ng/ml (Mean±SD) in the follicular phase and 11 0±3 3 ng/m (Mean±SD) in the luteal phase This difference is not significant and both levels are within the range found in normal women Bromocriptine suppressed prolactin in all patients but in all normoprolactinemic patients this suppression did not cause any statistically significant alteration in serum progesterone estradiol 17-β FSH or LH In one hyperprolactinemic patient (AS) increase in the luteal phase progesterone synthesis was accompanied by a normalization in the endometrial histology which had previously been diagnostic of luteal insufficiency Among the five patients with

normal hormonal secretion but with endometrial histology suggesting luteal insufficiency (JF BD LG IHO and MR) three achieved a normal histological picture during treatment

All the patients with infertility and a positive response to treatment with the exception of patient HF were given follow up treatment for three to five months but no pregnancies were achieved during the study Patient AS conceived one year later during continued bromocriptine therapy During the initial trial one patient (HF) developed a generalised urticarial rash after nine weeks treatment

DISCUSSION

The present study indicates the existence of prolactin dependent lutal insufficiency and shows that it is not merely found as a temporary phenomenon during inadequate prolactin suppression in patients with galactorrhea and amenorrhea as previously reported (3 10) It furthermore seems to exist irrespective of whether galactorrhea is present or not

It is well known that single cycles with luteal insufficiency do occur in normal women but in the present study hormone profiles during additional cycles confirmed the diagnosis of luteal insufficiency the prolactin levels and the positive response to ptine therapy in both hyperprolactinemic It is suggestive that both patients had some i of prolactin secretion but not the more hyperprolactinemia which is almost invaria associated with amenorrhea These data are completely in agreement with the findings of another study group (5) who describe four patients with short luteal phases infertility and prolactin concentrations between 35 and 48 ng/ml A recent publication (6) describes a modest but significant prolactin elevation among 11 patients with infertility and luteal phases of less than 12 days duration but normal progesterone and estradiol 17 β levels This finding may support the concept that even less pronounced prolactin elevations might interfere with normal luteal function

It is well documented that bromocriptine has no stimulatory effect on ovarian steroid secretion in normal menstruating women (4) but it has been shown (11) that bromocriptine can be used for induction of ovulation in many amenorrhoic patients even though they are normoprolactinemic In the present study bromocriptine restored normal luteal steroid secretion in two of five normoprolactinemic patients a finding which was confirmed in additional control and treatment cycles In these patients the absence of alterations in FSH and LH during treatment suggest a peripheral stimulation either mediated through lowering of circulating prolactin or through direct dopaminergic action

The improvement in endometrial histology noticed in three patients with normal hormonal profiles has not been confirmed by additional biopsies so even though premenstrual spotting was reduced in two of these during follow up treatment the lack of pregnancies either suggest that the finding might be incidental or that the patients had additional causes for infertility

ACKNOWLEDGEMENTS

The authors wish to thank Sandoz Copenhagen for the supply of bromocriptine (Parlodel[R]) and the National Pituitary Agency National Institute of Arthritis Metabolic and Digestive Diseases for providing the reagents to the prolactin radioimmunoassay

REFERENCES

1 Benedek Jaszmann L J & Hearn Sturtevant M D Premenstrual tension and functional infertility Lancet *I* 1095 1976
2 Bohnet H G Dahlen H G Wuttke W & Schneider H P G Hyperprolactinemic Anovulatory Syndrome J Clin Endocrinol Metabol *42* 132 1976
3 Corenblum B Pairaudeau N & Shewchuck A B Prolactin hypersecretion and short luteal phase defects Obstet Gynecol *47* 486 1976
4 del Pozo E Goldstein M Friesen H Brun del Re R & Eppenberger U Lack of action of prolactin suppression on the regulation of the human menstrual cycle Am J Obstet Gynecol *123* 719 1975
5 del Pozo E Wyss H Lancranjan J Obolinsky W & Varga L Prolactin induced luteal insufficiency and its treatment with brompcriptine Preliminary results Proc Symposium on Ovulation in the human Freiburg 10-12 9 1975 (Academic Press)
6 Fredricsson B Bjoerk G & Carlström K Short luteal phase and prolactin Lancet *I* 1210 1977
7 McNatty K P Sawers R S & McNeilly A S A possible role for prolactin in control of steroid secretion by the human Graafian Follicle Nature *250* 653 1974
8 Midgley A R Radioimmunoassay A method for human chorionic gonadotropin and human luteinizing hormone Endocrinology *79* 10 1966
9 Midgley A R Radioimmunoassay for human follicle stimulating hormone J Clin Endocr *27* 295 1967
10 Pepperell R J Evans J H Brown J B Smith Margery A Healy D & Burger H G Serum prolactin levels and the value of bromocriptine in the treat

ment of anovulatory infertility Brit J Obstet Gynaecol *84* 58 1977

11 Seppälä M Ranta T & Hirvonen E Bromocriptine treatment of secondary amenorrhea Lancet *1* 1154 1976

12 Tyson J E Andreasson Barbara Huth Janice Smith B & Zacur H Neuroendocrine Dysfunction in Galactorrhoea Amenorrhoea after oral contraceptive use Obstet Gynecol *46* 1 1975

Submitted for publication February 2 1978

Anders Nyboe Andersen M D
G 115
KAS Herlev
2730 Herlev
Copenhagen
Denmark

Acta Obstet Gynecol Scand 58 385 – 388 1979

SERUM TESTOSTERONE FSH/LH AND URINARY EXCRETION OF ESTROGENS AND CORTICOIDS DURING TREATMENT WITH AN INJECTABLE LONGACTING ESTROGEN DHEA PREPARATION

Henrik Nyholm and Rolf Plesner

From the Department of Gynecology and Obstetrics
Frederiksborg Amts Centralsygehus Hillerød Denmark

Abstract Ten weeks after total hysterectomy and bilateral salpingo-oophorectomy nine women were treated with injections of Gynodian[R] composed of 4 mg estradiol valerate and 200 mg dehydroepiandrosterone enanthate followed by injections of Primodian[R] composed of 4 mg estradiol valerate and 90 27 mg testosterone enanthate Before commencement of treatment estimation of serum FSH LH and testosterone and analyses for total estrogen 17 ketogenic steroids and fractionated 17 ketosteroids in 24-hour urine samples were carried out in all patients The same serum and urine analyses were made 2 weeks after the first Gynodian[R] injection and the first Primodian[R] injection respectively Serum testosterone concentrations did not change during treatment with Gynodian[R] whereas they rose markedly after administration of Primodian[R] Two weeks after the first injection of Gynodian[R] and also of Primodian[R] the total estrogen excretion was only slightly increased in comparison with the value measured before start of treatment and the serum FSH/LH ratio was only slightly depressed The daily urinary excretion of 17 ketogenic steroids and of fractionated 17 ketosteroids were unchanged during treatment

The risk of endometrial hemorrhage resulting from treatment of menopausal and postmenopausal women with estrogens particularly estradiol compounds is well known The risk is exacerbated by treatment *with long acting preparations such as oil suspensions* of estrogens which are less manageable than orally administered preparations Rieder stated that treatment with oil suspension preparations was accompanied by proliferative breakthrough bleeding in up to 10 per cent of the cases (11)

Testosterone however decreases the risk of hemorrhage by inhibition of endometrial proliferation Moreover due to the positive anabolic effect of testosterone a mixture of testosterone and estrogen allows a decrease in the estrogen dosage while yet maintaining the full remedial effect of estrogen Based on this beneficial relationship a combination of estradiol and androgen has been utilized for about twenty years The advantage of decreased risk of hemorrhage from such a preparation is unfortunately accompanied by risk of masculinization because all of the present preparations contain a testosterone ester Consequently efforts have been made to preserve the anti estrogenic effect of androgen on the endometrium but avoid the masculinizing effect of testosterone by employing an ester of dehydroepiandrosterone (DHEA) in place of testosterone ester *According to Rieder (11) Gerhards found after an in*jection of 200 mg tritium labelled DHEA enanthate that the plasma level was constant at the end of 2 3 days 28 per cent was excreted in the urine after 7 days and the compound was totally eliminated from the plasma after 24-44 days The greater part of the testosterone formed from DHEA enanthate was found to be bound to glucuronic acid Another investigation by Horton & Tait (5) reported that only 0 7 per cent of intravenously injected DHEA was converted into testosterone Zara (1971 unpublished) found that 50 per cent of injected DHEA was eliminated after 8 days and that 94 per cent of the injected ^{14}C labelled DHEA was excreted in the urine and 6 per cent in the faeces Following oral administration of *DHEA sulphate Kaiser et al (6) found a significant* rise in plasma and in urinary estrogen an increase in androstendione a fall in plasma cortisol but no measureable increase in plasma testosterone

The injectable long acting preparation Gynodian[R] consisting of 200 mg DHEA enanthate and 4 mg estradiol valerate per ml oil suspension has been employed by several authors in the treatment of women with menopausal symptoms Picha & Weghaupt (10) treated 266 postmenopausal women all of whom had been amenorrheic for at least one year Consecutive injections of Gynodian[R] were administered intramuscularly at 3 8 week *intervals for up to 6* years (average 17 months) Breakthrough bleeding occurred in 13 of the patients (4 8 per cent) during

Table I *FSH and LH in serum before and during treatment (mIU/ml)*

Case	FSH/ LH	One week be fore start of treatment	At time of 1st Gynodian[R] injection	Two weeks later	At time of 1st Primodian[R] injection	Two weeks later
1 A C	FSH	155	120	155	>213	208
	LH	55	66	39	48	36
2 L K	FSH	>150	>200	149	176	128
	LH	97	115	89	79	68
3 R F	FSH	169	197	—	123	79
	LH	78	63	—	45	30
4 I F	FSH	160	184	107	165	81
	LH	90	117	86	122	55
5 A M	FSH	203	193	83	147	189
	LH	77	69	35	88	63
6 K E	FSH	>200	>200	155	139	83
	LH	72	84	56	38	32
7 E H	FSH	73	104	57	94	59
	LH	42	40	25	33	14
8 B H	FSH	139	139	192	—	—
	LH	50	49	63	—	—
9 J H	FSH	—	—		—	—
	LH	—	—	—	—	—

treatment Histological examination of endometrium tissue obtained by scraping showed cystic glandular hyperplasia in 6 cases atrophy in 6 cases and slight proliferation in one case

Merger & Cohen (9) treated 70 menopausal women with intramuscular injection of Gynodian[R] every third to fifth week during a period of 2 26 months a of 1 005 months of treatment Breakthrough occurred in 15 cases (1 5 per cent) 10-20 days Rieder (11) treated 129 women suffer from menopausal symptoms with Gynodian[R] injections at 1 4 month intervals over a period of 2 years this investigation comprised 580 injections with an average of 4 5 injections per patient Break through bleeding occurred in 12 cases (0 3 per cent) Endometrium examinations revealed slight prolifera tion and cystic glandular hyperplasia respectively The treatment had excellent results in counteracting menopausal symptoms in 111 of the women (86 per cent) 10 achieved weak to moderate symptom relief (8 per cent) and 8 (6 per cent) obtained inadequate or no remedial effect The average duration of pharmacological effect was reported to be about 8 weeks

Caballero & Palomo (3) treated 150 women suffering from spontaneous or surgically induced menopause with consecutive injections of Gynodian[R] for a period of 4-12 months Symptomatic remission began 2 4 days after the first injection and the duration of pharmacological effect was found to be 15-47 days (average 26 4 days) This rather rapid remission of symptoms agrees well with an investigation by Kolb (8) who found that the maximal serum estradiol concentration following intramuscular injection of estradiol valerate was attained 2 days after injection Four days after injection the concentration was reduced to 50 per cent and after 10 days to 25 per cent No masculinizing effects were observed in any of the above mentioned investigations

In addition to its inhibition of endometrial proliferation testosterone exerts an anti estrogen effect on estrogenprimed vaginal epithelium causing fall in the number of superficial cells Holzner (4) treated 15 women by means of intramuscular 100 mg DHEA enanthate with 4 mg estradiol valerate suspended in 1 ml oil and 12 women with intramuscular 200 mg DHEA enanthate with 4 mg estradiol valerate (Gynodian[R]) Cytological examination of vaginal smears were performed the day before injection the day after injection and every third to fourth day thereafter for the following 4 weeks Little or no androgenic effect was found in vaginal epithelia after DHEA enanthate injection

The object of the present investigation was to compare the effects of Gynodian[R] on serum testosterone serum FSH and LH urinary estrogen excretion and adrenal cortical function with the effects of Primodian[R] in which the androgen component is a testosterone ester in place of the DHEA ester

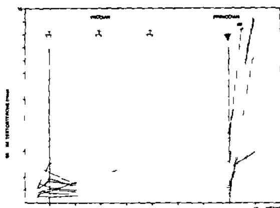


Fig 1 Serum testosterone levels of individual patients in relation to Gynodian^R injection and Primodian^R injection

MATERIAL AND METHODS

The patients who participated in this investigation were nine women 28 54 years of age all of whom had undergone total hysterectomy and bilateral salpingo-oophorectomy six cases for benign tumors (fibromas ovarian cysts) two cases with persistent bleeding under supplementary treatment with estrogens and one case of carcinoma in situ of the cervix uteri Pre-operatively five of the nine patients had menstruated regularly

Seven to twelve weeks after surgery (average 10 weeks) supplementary therapy with Gynodian^R was begun the schedule of which was a 1 ml injection every fourth week for a total of three injections Six weeks after the final Gynodian^R injection the supplementary therapy was shifted to Primodian^R with the injection schedule identical to the one described above One week before the first injection of Gynodian^R and also before Primodian^R at the time of the first injection and 2 weeks after the first injection in both cases the following analyses were carried out Serum testosterone according to the method of Buus (2) serum FSH and LH (2 IRP HMG) 24-hour urinary excretion of total estrogen according to the method of Brown *et al* (1) 17 ketogenic steroids (17 KGS) in 24-hour urine according to the method of Wilson & Lipsett (17) and fractionated 17 ketosteroids (17 KS) according to the gas-chromatographic method of Kampmann *et al* (7)

RESULTS

Due to a postal error the examinations for one patient (J H) consisted of only serum testosterone 17 KGS and fractionated 17 KS One patient at her own request withdrew from the investigation at the conclusion of Gynodian^R treatment

Effects on serum testosterone concentrations Serum testosterone concentrations before and after treatment are illustrated in Fig 1 During Gynodian^R treatment serum testosterone did not exceed the normal range for women (0 6-3 0 nmol/l) whereas after treatment with Primodian^R serum testosterone rose sharply from 0 7 5 4 nmol/l to 4 0-22 4 nmol/l

Effects on serum FSH and LH concentrations Fourteen days after injection of both Gynodian^R and Primodian^R serum FSH in most cases can be seen to decline slightly (Table I) as compared with the values recorded before starting the treatment In general the serum FSH remained at the postmenopausal level Serum LH declined slightly after injections of both preparations and there was a slight rise in one case only The post injection serum LH values also remained at a postmenopausal level

Effects on total estrogen excretion in 24-hour urine A slight increase in total estrogen excretion resulted from both Gynodian^R and Primodian^R treatment (Fig 2)

Effects on 24-hour urinary excretion of 17 KGS and of fractionated 17 KS Neither Gynodian^R nor Primodian^R treatment caused any change in the excretion of 17 KGS as compared with the values recorded before the start of treatment With regard to 17 KS a moderate rise in the E and A fractions were observed in one case after treatment with Gynodian^R in another case a moderate rise in DHEA and E fractions were found also following Gynodian^R treatment Apart from these two cases no changes in 17 KS were seen

Clinical effects The remedial effects on the patients clinical symptoms were excellent during both phases of the treatment programme and improvement occurred as early as 1 2 days after injection The duration of the pharmacological action in most cases was 21 23 days and up to 28 days in two cases No side effects such as masculinization were observed in any of the patients

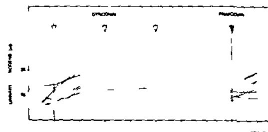


Fig 2 Excretions of total estrogens in 24-hour urine by individual patients in relation to Gynodian^R inject on and Primodian^R injection

DISCUSSION

Fourteen days after injection of either preparation total estrogen excretion was not essentially higher than the value recorded before the start of treatment This result coincides with the finding that serum gondadotrophin concentration 14 days after injection exhibited only a slight decrease compared to the values recorded before the start of treatment The observation that estrogen excretion was essentially unchanged *14 days after injection* is in good accordance with the investigation of Kolb (8) who found that the serum estrogen level had fallen to 25 per cent of its maximal concentration only 10 days after injection of estradiol valerate (the maximal level was reached 2 days after injection)

Curiously a beneficial effect which we cannot yet explain was that symptomatic relapse did not occur earlier than 21 days after injection despite the fact that the estrogen excretion had declined to the pre treatment level by 14 days after injections

Serum analyses clearly showed that Gynodian[R] as opposed to Primodian[R] caused no rise in the testosterone level Accordingly treatment with Gynodian[R] can be assumed to involve no risk of masculinizing effect

Since the patients in this investigation had undergone hysterectomy it was not possible to ascertain whether Gynodian[R] exerts an anti estrogen effect on the endometrium as does Primodian[R]

ACKNOWLEDGEMENTS

iodian[R] and Primodian[R] were kindly donated by Schering Kemi A/S

REFERENCES

1 Brown J B MacLeod S C Macnaughton C Smith M A & Smyth B A rapid method for estimating oestrogens in urine using a semiautomatic extractor J Endocrinol *42* 5 1968

2 Buus O Determination of testosterone in human plasma by means of double isotope derivative technique Acta Endocrinol (Kbh) Suppl 138 1969

3 Caballero A & Palomo A Treatment of the climacteric with a new oestrogen androgen combination Toko-Ginecologia Practica *322* 507 1973

4 Holzner J H Untersuchungen über den Einfluss einer Östrogen Kombination auf das Vaginalepithel Medizinische Mitt *32* 27 1971 (ed Schering AG Berlin)

5 Horton R & Tait J F In vivo conversion of dehydroisoandrosterone to plasma androstenedione and testosterone in man Clin Endocrinol Metabol *27* 79 1967

6 Kaiser E Schmidt Elmendorf H Crabben H van der & Gerteis W Treatment of climacteric difficulties with an estrogen precursor Arch Gynäk *211*(1 *) 183 1970

7 Kampmann J P Jørgensen F S Bennett E P & Johnsen S G Rise in DHEA and estrogens during clomiphene administration in normal men Acta Endocrinol (Kbh) *83* 166 1976

8 Kolb K H & Schulze P E Pharmacokinetics of sexual steroids in man *In* Symposium of sexual steroids in Bogoth 1968 Verlag Saladruck Berlin (1969)

9 Merger R & Cohen J Étude clinique d une association hormonale de valérianate d oestradiol et d oenenthate de déhydroepiandrostérone sur les troubles de la menopause Comptes Rendue Société Francaise Gynécologie *42* 472 1972

10 Picha E & Weghaupt K A new hormone combination for menopausal complaints Med Klin *67* 382, 1972

11 Rieder E Zur Therapie klimakterischer Störungen Wien Med Wochenschr *122* 317 1972

12 Wilson H & Lipsett M B Use of periodate oxidation in clinical analysis of urine corticoids Anal Biochem *5* 217 1963

Submitted for publication August 17 1978

Henrik Nyholm M D
Department of Obstetrics and Gynecology
Frederiksborg Amts Centralsygehus
Hillerød
Denmark

Acta Obstet Gynecol Scand 58 389–391 1979

UTERINE AND OVARIAN ESTROGEN RECEPTOR LEVELS IN CLIMACTERIC WOMEN

R Punnonen I Kouvonen T Lövgren and L Rauramo

From the Department of Obstetrics and Gynecology University of Turku and the Department of Biochemistry and Pharmacy Åbo Akademi Turku Finland

Abstract High affinity cytoplasmic estrogen receptors in the endometrium myometrium and ovary of 15 climacteric women were studied In addition the concurrent serum estradiol and progesterone level of each woman was estimated and the endometrium examined histologically The cytoplasmic estrogen receptor level of the endometrium and myometrium had remained extremely high in some cases several years after the menopause and in the presence of a completely atrophied endometrium The lowest endometrial and myometrial estrogen receptor levels in premenopau al women were measured towards the end of the menstrual cycle The endometrial estrogen receptor level was roughly 2–3 times the comparable myometrial level Estrogen receptors were also encountered in all cases in the cervical myometrium The estrogen receptor levels of the ovary were low in all cases

An outstanding event in the climacteric is the reduction of ovarian function The function of the corpus luteum is dusturbed initially and anovulatory cycles become common The consequence may often be a hyperestrogenic condition with prolongation of the proliferative phase Estrogen production by the ovary also gradually diminishes and no longer suffices to stimulate the endometrium and the menopause takes place The ovaries may excrete estrogens to some extent even after the menopause

Hormonal effects are transmitted to the tissues and cells via hormone receptors Both estrogens and progesterone are known to affect estrogen receptors Our aim was to study uterine and ovarian estrogen receptor levels in the climacteric a time when there are exceptionally great changes in the estrogen and progesterone concentrations

SUBJECTS AND METHODS

Uterine and/or ovarian estrogen receptor levels were studied in 15 patients aged 40–59 years (mean 50 6 years) Most of the women were pre-menopausal but their menstrual cycles were already irregular Many of the patients had climacteric symptoms Hysterectomy was generally performed for myomas and in several cases oophorectomy was undertaken at the same time Specimens for histological examination were taken immediately after the hysterectomy or oophorectomy The uterus and ovary were cooled to 0–4 C on ice The endometrium was separated from the myometrium Receptor determination was performed from the whole myometrium of the uterine body which was dissected into small parts The ovary was halved in the longitudinal ascis one half was sent for histological analysis while receptors were determined from the other half

The pieces of tissue were frozen in liquid nitrogen within 30–60 min of hysterectomy and were stored at −20 C Furthermore in the majority of the cases a blood sample was taken from the peripheral vein immediately preoperatively for serum estradiol and progesterone determinations Estradiol was determined according to Hotchkiss (6) and progesterone according to De Villa s (3) method

The tissue pieces were thawed in physiological saline at 0–4 C rinsed once and then rinsed twice in Tris HCl buffer (40 mM Tris HCl buffer pH=7 4) Finally four volumes by weight of the buffer were added Homogenisation was carried out with an Ultra Turrax TP 18/10 shaft 10 N homogeniser 5–6 times each for 15 sec on ice at intervals of 1 min The homogenate was centrifugated for 1 hour at 108 000 xg at 4 C And the supernatant (cytosol) was used for receptor determination

Six different concentrations 8 4 2 1 0 5 0.25 nmol/l of 2 4 6 7-^{3}H-estradiol (100 9 Ci/mmol) in 100 µl of Tris-HCl buffer and 100 µl of cytosol were pipetted into test tubes in an ice bath In addition a second series containing a 100-fold excess of cold estradiol was prepared for the determination of nonspecific binding The tubes were incubated for 1 hour at +30 C for determination of the total estrogen receptor concentration in the cytosol

After incubation the tubes were cooled rapidly in an ice bath and 500 µl of dextran-charcoal suspension (0 5 per cent activated charcoal and 0 05 per cent dextran in buffer) was added to remove the unbound estradiol The tubes were incubated again for 15 min at 0 C in an ice bath and then centrifuged for 15 min at 800 xg A 500 µl sample was transferred from the supernatant into a scintillation flask 10 ml of scintillation fluid was added and counted for 5 min with an LKB-Wallac 81000 liquid scintillation counter

Proteins were determined by Lowry's method (8) The dissociation constant and binding capacity were determined graphically according to Scatchard (13)

Table I *Data regarding patients the stage of the menstrual cycle at which hysterotomy was performed the concentration (fmole/mg protein) of cytoplasmic estrogen receptor sites the dissociation constant (nM) for the estrogen receptor complex in cytosol from ovary myometrium and endometrium and the concentration (nmole/l) of estradiol and progesterone in serum*

Patient	Age	Time from last menstr	Ovary Receptor conc	Ovary K_D	Myometrium Receptor conc	Myometrium K_D	Endometrium Receptor conc	Endometrium K_D	Histology	Serum Estradiol	Serum Progesteron
L O	51	20 days	2	0 07	60	1 02	162	0 12	M h c	0 90	< 5
A L	49	30 days	1	0 21	28	0 13	65	0 20	Prolif	0 40	< 5
H U	55	10 years	15	0 04	—	—	400	0 40	Atrophic	<0 20	< 5
E H	48	8 days			47	0 22	640	0 67	Weak prolif		
T P	48	18 days			52 1	1 27			M h c	0 52	< 5
S S	40	8 days			71	0 26	138	0 17	Prolif		
M S	52	7 days	1	0 15							
J F	50	20 days	5	0 28			45	0 36	Secr	0 79	38
R M	59	10 years	2	0 23	147	0 39			Atrophic	<0.20	< 5
L N	56	5 months	4 8	0 73	458	0 29			Atrophic	<0 0	< 5
E K	54	1 years	12 7	0 35	35	0 27	90 1	0 18	Atrophic	<0 20	< 5
					cervix 23	0 38					
A H	48	9 months	—	—	42	0 26			Weak prolif	<0 20	< 5
					cervix 59	0 22					
S N	40	17 days	6 0	1 81	63 4	0 47			St intermed	0 60	29
					cervix 47 8	0 43					
T L	54	4 years	9 8	0 21	180 4	0 18			Atrophic	<0 20	< 5
					cervix 64 6	0 56					
A L	55	5 years			205		695		Atrophic	<0 20	< 5
					cervix 254						

RESULTS

The results are presented in table I The cytoplasmic estrogen receptor level of the endometrium and had remained high in some cases several after the menopause The concentration of in the endometrium was 2−3 times that in myometrium This was valid also for the high receptor concentration of atrophic endometrium Compared with endometrium and myometrium ovarian receptor levels were low in all cases

DISCUSSION

The estrogen receptor concentration of human endometrium has been determined from both homogenate and tissue section during different phases of the menstrual cycle The results reported in the literature are contradictory Evans *et al* (5) obtained the highest estrogen receptor levels during the cycle from endometrial homogenate in the proliferative phase (2−5 days from the beginning of the menstrual cycle) and the lowest concentrations premenstrual Tissue sections have displayed higher concentrations in the proliferative than in the secretory phase although the levels during the early proliferation phase were low (4) High concentrations in the early proliferation phase however were observed by Maass *et al* (9)

Conversely Robertson *et al* (11) recorded the highest concentrations around the middle of the cycle and the lowest at its beginning and end Crocker *et al* (2) also reported that the estrogen receptor concentration was at its highest at the time of ovulation in both cytoplasm and nucleus

Bayard *et al* (1) studied the variation of the total estrogen and progesterone concentration and of both the cytoplasmic and nuclear receptor concentration in endometrial biopsy specimens during the menstrual cycle The results support the view that hormones exert a receptor inducing effect and that progesterone lowers the estrogen receptor concentration The ratio between cytoplasmic and nuclear receptors is distinctly dependent on hormone concentration Definitely declining estrogen receptor concentrations have been recorded during the luteal phase The explanation may be found in considering the action of progesterone Progesterone is known to reduce the sensitivity of the uterus to estrogen and to lowere the estrogen receptor level of cytosol (7 14) According to our own study the estradiol receptor level was also lower at the end of the menstrual cycle

Overall the estrogen receptor concentration of

cytosol is influenced by opposing factors and the final concentration depends upon the balance between them Estrogen stimulation increases the numbers of estrogen receptors in cytosol On the other hand estrogens decrease the amount of cytoplasmic receptors as the estrogen receptor complex is formed and transferred to the nucleus As no exact information is available on the rate of effect of progesterone and estrogen hormones and on their ratio interpretation of results is often difficult This apparently explains the contradictory results reported in the literature

The extremely high endometrial and myometrial receptor concentrations in the presence of a postmenopausal fully atrophied endometrium which were observed in our study were rather surprising Similar cases have however been described by Evans *et al* (5) The dissociation constant shows that the receptors preserved their high hormone affinity As the hormone concentrations are low it can be assumed that the majority of the receptors are in cytosol (1) It is probable that receptor synthesis is both constitutive and induced McGuire *et al* stated however that they had encountered similar concentrations in endometrial myometrial homogenate in both pre and postmenopausal uteri (10) We observed a high receptor concentration in the endometrium of one patient but no myometrial receptors (case H U) The sensitivity of endometrium to estrogen is evidently also preserved in cases in which the endometrial estradiol receptor concentration remains high after the menopause The clinical significance of this is difficult to evaluate However it is obvious that endometrial proliferation is induced more easily than usual in these cases by exogenous estrogens

According to Robertson *et al* (11) no receptors can be found in the cervix The cytosol from cervix contained however estrogen receptors in all the five cases we studied in two cases the concentrations were even higher than in the myometrium Our results lend support to the observation made by Sanborn *et al* (12) that the cervix estrogen receptors which resemble those of the corpus in their properties

REFERENCES

1 Bayard F Damilano S Robel P & Baulieu E E Récepteurs de l oestradiol et de là Progestérone dans l endomètre humain au cours du cycle menstruel C R Acad Sc Paris *281* 1341 1975

2 Crocker S G Milton P J D & King R J B Uptake of (6 7-^{3}H) Oestradiol 17β by normal and abnormal human endometrium J Endocr *62* 145 1974

3 DeVilla G O Roberts K Wiest W G Mikhail G & Flickinger G A specific radioimmunoassay of plasma progesterone J Clin Endocrinol Metabl *35* 458 1972

4 Evans L H & Hähnel R Oestrogen receptors in human uterine tissue J Endocr *50* 209 1971

5 Evans L H Martin J D & Hähnel R Estrogen receptor concentration in normal and pathological human uterine tissues J Clin Endocrinol Metab *38* 23 1974

6 Hotchkiss J Atkinson L E & Knobil E Time course of serum estrogen and luteinizing hormone (LH) concentrations during the menstrual cycle of the rhesus monkey Endocrinology *89* 177 1971

7 Hsueh A J W Peck E J Jr & Clark J H Control of uterine estrogen receptor levels by progesterone Endocrinology *98* 438 1976

8 Lowry O H Rosebrough N J Farr A L & Randall R J Protein measurement with the folin phenol reagent J Biol Chem *193* 265 1951

9 Maass H Bruemmer P Egert D Engel B Hohmeister H Lehmann F & Trams G On the existence of receptors for estradiol in normal and malignant human tissue and the mode of action of progesterone Acta Obstet Gynecol Scand Suppl 19 p 30 1971

10 McGuire J L Bariso C D Fuller B S McElrath T G & Delahunte J M Preliminary isolation of an estrogen specific binding macromolecule from the human uterus J Clin Endocrinol Metab *34* 243 1972

11 Robertson D M Mester J Beilby J Steele S J & Kellie A E The measurement of high affinity oestradiol receptors in human uterine and myometrium Acta Endocrinol *68* 534 1971

12 Sanborn B M Held B & Kuo H S Specific estrogen binding proteins in human cervix J Steroid Biochem *6* 1107 1075

13 Scatchard G The attractions of proteins for small molecules and ions Ann N Y Acad Sci *51* 660 1949

14 Tseng L & Gurpide E Effects of progestins on estradiol receptor levels in human endometrium J Clin Endocrinol Metab *41* 402 1975

Submitted for publication February 2 1978

Reijo Punnonen M D
Department of Obstetrics and Gynecology
University Central Hospital
SF ?05?0 Turku 52
Finland

ANNOUNCEMENT

The Center for Disease Control the International Union Against the Venereal Diseases and Treponematoses and other national and international agencies are sponsoring an ***International Symposium on Pelvic Inflammatory Disease*** (PID) on April 1 3 1980 in Atlanta Georgia Scientific papers will be presented on clinical and laboratory aspects of diagnosis management and the epidemiology management and control of PID

Abstracts Abstracts related to the topics above should not exceed 250 words and should describe the study methods results and conclusions They should be submitted no later than December 1 1979 to
Center for Disease Control
Attention Symposium Director
International Symposium on Pelvic Inflammatory Disease
Building 1 Room 3070
Atlanta Georgia 30333

Financial assistance may be available for individuals whose abstracts are accepted

Proceedings of the Symposium will be published in a referred scientific journal

Attendance Those interested in attending the meeting should notify the Symposium Director (above address) by February 1 1980 since seating and accommodations are limited

International symposium on uterine and placental blood flow will take place at the University of Chicago Center for Continuing Eduction Chicago Illinois March 24-25 1980 *Sponsored by Chicago Heart Association and the University* of Chicago Department of Obstetrics and Gynecology Supported by the National Institutes of Health

The program will include speakers from various disciplines of medicine Discussion will stress methodology physiological and pharmacological influences on blood flow and various stress factors Speakers will be investigators in the field of vascular smooth muscle in general and uterine and placental blood flow in particular The program is intended to summarize recent research and critically review the subject Attendance is limited to 100 on a first-come first serve basis

Category I AMA Physician Recognition Award credit hours and Cognates from the American College of Obstetricians and Gynecologists have been applied for

For further information contact
Susan A Shekelle
Section Head
Preventive Cardiology
Chicago Heart Association
20 North Wacker Drive
Chicago Illinois 60606
USA

Acta Obstet Gynecol Scand 58 393–399 1979

WATER AND ION METABOLISM IN PLACENTA

II Water compartments and electrolytes in slices of rabbit placenta at different periods of gestation incubated at 0-1 C

A Cittadini F Castaldo P Paparella R Romor G Carelli A Bompiani and T Terranova

From the Institutes of General Pathology and Obstetrics and Gynecology Catholic University School of Medicine Rome Italy

Abstract The movement and the distribution of water sodium potassium chloride magnesium and calcium have been studied in slices prepared from rabbit placentae at different periods of gestation incubated in condition of depressed metabolism (0-1 C) In these conditions the tissue takes up water from the external medium up to a maximum of about 2 0 kg/kg d wt which represents 30 per cent of the initial H_2O content of the fresh tissue The extracellular compartment swells progressively and proportionally to the age of the placenta The sodium and chloride content of the tissue increases while that of potassium decreases and their intracellular concentration reaches after 120 min that of the external medium Magnesium does not show appreciable changes and calcium too despite its extreme variability does not seem to undergo significant variations during the cold incubation

The results obtained show that placenta like most of other mammalian cell systems possesses specific metabolism dependent mechanisms responsible for the maintenance of water distribution and ion gradients among the different tissue compartments The characteristics and the regulation of these mechanisms are discussed in detail

Placenta cells are able to maintain *in vivo* a high content of potassium and a low content of sodium and chloride (1) Experiments that alter tissue metabolism could give more information on the regulation of the electrolytes and cell volume of this organ This information might be particularly useful in relation to the filter and active transport function of placenta

In this paper we study the water and ion distribution in slices from rabbit placentae at different periods of gestation in conditions of strongly inhibited metabolism Such conditions have been achieved by incubating the slices in Ringer solution kept at 0-1 C a temperature at which metabolism is almost stopped while the integrity of the tissue is preserved This procedure does not cause any irreversible damage to the tissue and makes possible the subsequent study of the recovery of cell water and ion gradients by simply modifying the incubation conditions (e g by warming to 38 C) (see accompanying paper) This experimental design has already given interesting information on other mammalian tissue (2 3 5)

MATERIAL AND METHODS

Pregnant white giant New Zealand rabbits were obtained at known days of gestation and kept on standard diet Some animals were brought beyond the physiological term of their gestation by daily subcutaneous injection of 1000 I U of HCG The animals arbitrary subdivided into five groups on the basis of their gestation age were treated and killed as previously described (1) After exsanguination the pregnant uterus was quickly dissected and the placentae were carefully freed from all contaminating tissues (endometrium and membranes) and areas of necrosis The placentae were then placed on a moistened filter paper (Whatman hardened no 54) held on a Petri dish containing crushed ice Slices were cut freehand approximately 0 2-0 4 mm thick with a razor blade (Thomas) guided by a glass slide Tissue slices were briefly rinsed in 15 20 ml of cold isotonic buffered saline and placed in a flask containing a suitable amount of medium (see composition below) previously chilled and kept at 0-1 C in an ice bath

The incubation medium used throughout the experiments had the following composition Na^+ 158 mM K^+ 5mM Ca^{2+} 1 3 mM Mg^{2+} 1 0 mM SO_4^{2} 1 0 mM Cl 175 6 mM and Tris HCl pH 7 4 10 mM (Ringer Tris)

After the incubation tissue slices samples taken at time intervals were gently blotted on filter paper and placed in tared plastic bottles The wet weight (w wt) of the slices was then determined and the samples were thereafter dried over night in oven at 80 C The day after the bottles after a suitable period of equilibration in a dessicator at room temperature were weighed again in order to determined the dry weight (d wt) of the sample and to calculate the amount of total tissue water (H_2O_{tot})

The size of tissue water compartments was determined in the rabbit placental slices using inulin as a marker for the extracellular space For this purpose tissue slices were incubated in the same medium as above but containing in addition 0 5 per cent inulin and then extracted in 6 per cent PCA (perchlorid acid) Inulin was determined colorimetrically following Kulka (4) and a blank was used to compen

Table I *Total water (H_2O_{tot} in kg/kg d wt) content of placenta slices at different periods of gestation in cubated in Ringer – Tris at 0 – 1 ° C for different extent of time Data given as Mean ± S E M followed by No of observations (in petit)*

Gest	Time of incubation at 0 – 1 C (min)											
period	0	15	30	60	90	120	150	180	240	300	360	mean[b] %
I	6 2± 3 44	—	6 1± 4 8	6 2± 4 8	6 5± 5 7	7 2± 5 8	—	7 4± 4 6	7 4± 4 8	7 6± 5 8	—	+19
II	5 5± 06 31	6 4± 2 9	6 7± 3 11	6 5± 2 14	7 0± 2 14	7 0± 1 26	7 0± 3 11	7 2± 3 5	7 1± 4 6	7 5± 08 6	7 6± 3 4	+35
III	5 2± 09 17	6 2± 3 8	6 3±.2 8	6 1± 4 6	6 4± 4 8	6 6± 4 8	6 5± 3 8	6 9± 2 8	7 2± 3 8	7 2± 2 8	7 3_.3 7	+35
IV	5 4± 07 14	6 1± 1 6	6 2± 2 6	6 7± 2 6	6 2± 1 6	6 8± 2 6	6 9± 1 6	6 8± 2 6	7 1± 3 6	7 1± 2 6	7 3± 2 6	+30
V	5 1± 1 24	5 3± 2 6	5 7± 2 6	5 6± 3 6	5 6± 2 6	6 4± 2 8	6 2±.2 6	5 9± 3 6	6 2± 3 6	6 3± 3 6	6 5± 2 4	+24

Data taken from ref no 1

[b] Total water mean per cent increase related to the fresh tissue (0 time) cal-ulated from the data of the interval 120 – 360 min

sate for color due to endogenous material The results have been expressed as α inulin that is the ratio tissue H_2O con taining inulin at the same concentration as the medium/ H_2O_{tot} Thus the size of the extracellular compartment is easily obtained by the expression extracellular water (H_2O_e) = H_2O_{tot} × α inulin Intracellular water (H_2O_i) is obtained by difference

The amount of tissue sodium potassium calcium and magnesium was determined by atomic absorption spec trophotometry on the dry tissue after extraction with O 1N HNO_3 as previously described (1) Chloride was determined on the same extract following Zall *et al* (8)

RESULTS

- I summarizes the tissue water content of slices abbit placentae at different periods of gesta for different times in ice-cold (0-1 C) Tris solution For comparison the first col umn shows the water content of the fresh tissue (from ref 1) It can be clearly seen that tissue water in creases progressively and reaches at about 120 min a value about 25 35 per cent higher then that at zero time (fresh tissue) and that thereafter it remains stable at that level for the following four hours of incuba tion in the cold The same data are also plotted in the upper curves of Fig 2 The last column of table I shows the mean per cent incrase of tissue water at the different periods of gestation It is apparent that apart from period I the younger the tissue the higher the amount of water taken up

The inulin space (α inulin) of the placenta in cubated for 6 hours in the isotonic buffered saline at 0-1 C is plotted for each period of gestation in the fig 1 It can be seen that α inulin reaches equilibrium at about 60 min of incubation at a value of 0 4 From these data and from those reported in table I (H_2O_{tot}) the water volume of the intra and ex tracellular compartments have been calculated the results are reported in table II and plotted together with H_2O_{tot} in fig 2 (lower cures) During the first two hours of incubation H_2O_i increases consistently in all the five periods and remains at the same level therafter On the other hand H_2O_e after a short period of equlibration (see fig 2) due to the inulin permeation into the tissue stabilizes at a value equal to that of the fresh tissue In the two last columns of table II the mean per cent variations of the two com partments are reported As already mentioned H_2O_e shows only small inconsistent changes whereas H_2O_i increases strongly in all the periods considered (by about 50 per cent in the two first periods and by 80-97 per cent in the last) proportionally to the age of the placenta

The tissue content of sodium potassium chloride and magnesium in placenta slices incubated at 0-1 C for different extents of time is reported in fig 3 Both sodium and chloride increase sharply during the first 60 min at 0 1 C and reach values of about 1 000 mmol/kg d wt whereas potassium decreases to about 100 mmol/kg d wt The upper graphs refer to the content of magnesium This bivalent cation does not show any significant change during all the time of in cubation at 0-1 C being stable at the same value of the fresh tissue

From the knowledge of the size of the water com partments (table II and fig 2) and of the electrolyte content we have been able to calculate the in tracellular concentration of sodium potassium and chloride ($[Na^+]_i$ $[K^+]_i$ and $[Cl^-]_i$) these are plot ted in fig 4 It is evident that after 60 min of cold in cubation the $[Na^+]_i$ is equal to that of the external medium (thin horizontal line in fig 4) On the con trary neither K^+ nor Cl^- equilibrate with the medium In fact potassium does not decrease below

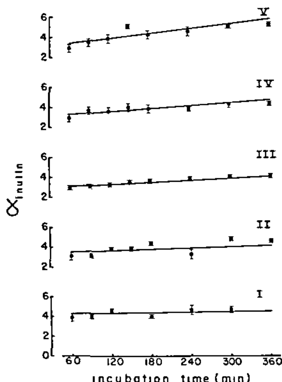


Fig 1 α inulin determined in slices from rabbit placenta at different periods of gestation incubated in Ringer Tris at 0-1 C From the lower part of the fig the values of α inulin ±SEM regarding the period I II III IV and V of gestation are reported

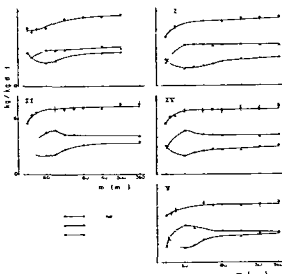


Fig 2 Time course of total water (H_2O_{tot}) extracellular water (H_2O_e) and intracellular water (H_2O_i) content of slices from rabbit placenta at different periods of gestation (I II III IV and V) during incubations in ice-cold Ringer Tris The amount of H_2O_i and H_2O_e have been calculated from the values of the H_2O_{tot} and of the α inulin (see also table I and fig 1) The values of intra and extracellular compartment at time 0 (fresh tissue) have been taken from ref no 1

30-35 mM (vs the external conc of 5 mM) and chloride does not exceed 100 mM (vs the external conc of about 175 mM) Our explanation for this phenomenon will be given later on

On the basis of the assumption that in the abscence of metabolism a chemical equilibrium should take place across the placenta cell membrane we calculated the net balance of positive and negative charged electrolytes at the two sides of cell membrane As predicted by the Donnan equation in the absence of energy metabolism the sum of positive charges should be equal to that of the negative ones at both sides of the cell membrane It appears clearly from fig 4 that this is not true for placental slices in contrast with the findings of others on different tissues systems (7) Indeed potassium and especially chloride both highly diffusible ions do not reach a concentration inside the cell equal to that of the external medium In particular our calculations gave evidence for an excess of negative charge inside the cell which can be explained by assuming the presence of a certain amount of fixed undiffusible negative charge inside the cell (e g anionic proteins) Fig 5 shows the plot of such anionic charges calculated to be present in placenta cells from the data of ionic equilibria achieved during the cold incubation of the slices in isotonic Ringer Tris It can be seen that their amount is constant at all the periods of incubation considered Their concentration is equal to about 60-70 m equiv/kg H_2O_i

The last fig 6 shows the calcium content of placental slices during 6 hours of incubation in the ice-cold medium This cation is very variable so that no conclusion can be drawn from these experiments The solid lines in the graph represent the linear regression lines calculated by the least squeares method in an attempt to detect any possible variation of this cation This method does not allow the behavior of this cation at 0-1 C to be defined while the increase of placenta calcium in relation to the period of gestation is confirmed (1)

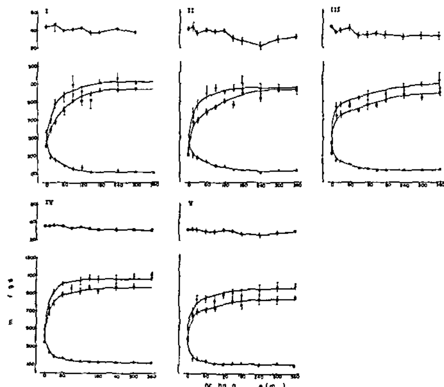


Fig 3 Sodium (•) chloride (□) potassium (Δ) and magnesium (O) content of slices from rabbit placenta at different periods of gestation during incubations at 0-1 C in ice cold buffered saline

DISCUSSION

Placenta water compartment at 0-1°C Slices from rabbit placenta at different periods of gestation in in an artificial buffered saline solution at show peculiar modifications in water distribu ong the different tissue compartments which to show cell edema Total tissue water in creases in the slices from placentae of all gestational groups less in the period I (19 per cent) and more in the following (25 30 per cent) More significant changes are related to the distribution of the water taken up by the tissue The extracellular compart ment remains almost unchanged during the incuba tion whereas the intracellular compartment increases by up to 100 per cent in the beyond term placentae (table II fig 1) The swelling of the intracellular com partment accounts completely for the volume of water taken up by the tissue Furthermore the cells from the older placentae are able to swell more than the younger even if the total tissue water content i.e lower in the former ones It is important to note that the size of the extracellular space obtained in this

Table 2 *Extracellular (H_2O_e) and intracellular (H_2O_i) water (kg/kg d wt) compartments of rabbit placenta slices at different periods of gestation incubated in Ringer–Tris at 0–1 C*

Gest	Time of incubation at 0–1 C (min)															
	0[a]		120		150		180		240		300		360		mean %	
period	H_2O_e	H_2O_i[b]	H_2O	H O	H_2O	H_2O	H_2O_e	H_2O	H_2O_e	H_2O_i	H_2O_e	H_2O_i	H_2O_e	H_2O	H_2O_e	H_2O_i
I	3 6	2 6	3 3	3 9			3 0	4 4	3 5	3 9	3 6	4 0			−10	+56
II	2 7	2 8	2 7	4 3	2 7	4 3	3 2	4 0	2 3	4 8	3 6	3 9	3 5	4 1	+11	+51
III	2 8	2 4	2 2	2 4	2 3	4 2	2 6	4 3	2 8	4 4	2 9	4 3	3 0	4 3	− 6	+80
IV	3 1	2 3	2 5	4 3	2 8	4 1	2 6	4 2	2 6	4 5	3 0	4 1	3 1	4 2	−11	+84
V	3 4	1 7	2 5	3 9	3 2	3 0	2 5	3 4	2 8	3 4	3 1	3 2	3 3	3 2	−15	+97

Data taken from Ref no 1
[b] Extracellular (H_2O) and intracellular (H_2O) water compartments have been calculated from the content of H_2O of the slices (Tab 1) and the α inulin (Fig 1)

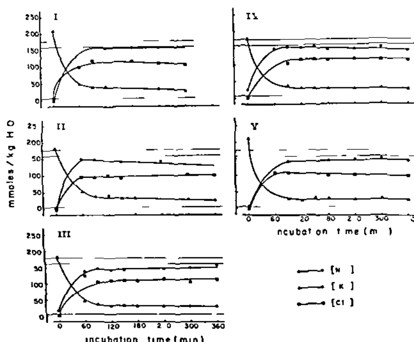


Fig 4 Intracellular concentration of Na^+ K^+ and Cl (mM) in rabbit placenta slices at different periods of gestation incubated in Ringer Tris at 0-1 C These data have been calculated from the values of H_2O_{tot} (table I) and total slices electrolytes content (fig 3) The thin horizontal lines a b and c refer to the medium sodium potassium and chloride concentration respectively For further details see the text

study from inulin distribution agrees closely with those calculated in fresh tissue from chloride distribution (1 and fig 1)

On the basis of the data presented here we can conclude that placental cells are able to regulate their water content by mechanisms linked to cell metabolism and which require energy At 0-1 C when tissue metabolism is greatly reduced the cell water content is regulated simply by the osmotic pressure of the intracellular solutes but these are themselves modified by eneregy failure (see below) In addition the cell volume can still double in the over term placentae even if total tissue water content is reduced

Ion distribution in placenta at 0-1 C Ionic gradients in placenta cells are considerably modified by incubating the tissue at 0-1 C In a previous paper we have reported that placental cells are able to maintain *in vivo* probably by energy expenditure the ionic gradients across their plasma membranes $[Na^+]_i$ and $[Cl^-]_i$ being low and $[K^+]_i$ high (1) In the conditions of the experiments described here the cell ionic situations is rearranged After 30-60 min of incubation at 0-1 C both total tissue and intracellular sodium and chloride increase while potassium decreases In the case of placental cells the ionic equilibrium reached in cold cannot be described by a simpled Donnan equilibrium for diffusible ions since the experimental data show that neither potassium nor chloride are perfectly equilibrated with the external medium whereas sodium is An explanation of this phonomenon can be found for potassium by assuming that the excess of this ion is bound to intracellular structures (7) and for chloride by assuming the existence of intracellular fixed anionic charges (proteins)

As far as the monovalent ions distribution is concerned we can conclude that when metabolism is strongly inhibited (0-1 C) the physiological gradients

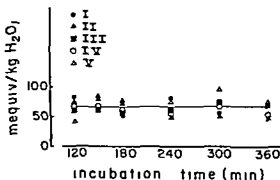


Fig 5 Intracellular concentration of fixed anions in slices from rabbit placenta at different periods of gestation incubated in an ice-cold Ringer Tris for different extent of time For explanation see the text

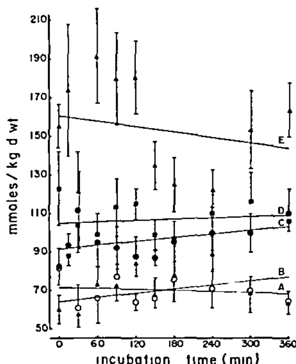


Fig 6 Calcium content of rabbit placenta slices at different periods of gestation (I II III IV V) incubated in Ringer Tris at 0-1 C The lines A B C D and E drawn across the different points represent the regression lines calculated by the least square methods See the text fur further explanation

lacental cell membrane are markedly altered rection of osmotic equilibration (loss of K^+ in of Na^+ and Cl)

As shown in the Results the magnesium content of the placenta does not change during the cold incubation in all the periods of pregnancy considered The intracellular and extracellular concentrations of magnesium remain at the same level as in the fresh tissue irrespective of the metabolic condition of the tissue On the basis of these findings we can conclude that all the placental cell magnesium is in a bound form and hence not free to diffuse along the concentration gradient (6)

In cold incubated placental slices calcium behaves similarly to magnesium Its concentration despite the extreme variability can be considered almost constant during the incubation at all the gestation periods studied Following the same line of reasoning as for magnesium calcium can also be considered to be mostly bound to intracellular structures (6)

The data presented in this paper can be summarized as follows When placental tissue is incubated at 0-1 C the total water of the tissue increases mainly by swelling of the intracellular compartment which in the over term placentae can double in volume The intracellular concentration of sodium reaches equilibrium with the medium while potassium decreases to very low levels Chloride on the other hand equilibrates across placenta cell membrane to the extent allowed by the concentration of fixed intracellular anionic charges Except for the movement of water which increases with the period of gestation of the placenta we did not find differences among the different periods of gestation as far as passive electrolytes movements are concerned

Further studies are in progress which are examining the recovery of the tissue when returned to metabolically favorable conditions The metabolic requirements and efficiency of the processes that maintain water and ion gradients in placental cells at different stages of growth and ageing are also being investigated

ACKNOWLEDGEMENTS

This work has been supported by Grants and Contribution from CNR of Italy Our thanks are due to the Institute of Occupational Medicine for making available the Atomic Absorption facility

REFERENCES

1 Cittadini A Paparella P L Castaldo F Romor R Polsinelli F Carelli G Bompiani A & Terranova T Water and ion metabolism in placenta I Water and ion content of rabbit placenta in different periods of gestation Acta Obstet Gyencol Scand 56 233 1977
2 Elshove A & Van Rossum G D V *Net movements* of sodium and potassium and their relation to respiration in slices of rat liver incubated in vitro J Physiol (London) *168* 531 1963
3 Heckman K D & Parsons D S Electrolyte distribution between rat liver slices and an artificial saline medium Biochim Biophys Acta *36* 213 1959
4 Kulka R G Colorimetric estimation of ketopentoses and ketohexoses Biochem J *63* 542 1956
5 Van Rossum G D V Net sodium and potassium movements in liver slices prepared from rats of different foetal and postnatal ages *Biochim Biophys* Acta *74* 1 1963
6 Van Rossum G D V Net movements of calcium and magnesium in slices of rat liver J Gen Physiol *55* 18 1970

7 Van Rossum G D V Gosalvez M Galeotti T & Morris H P Net movements of monovalent and bivalent cations and their relation to energy metabolism in slices of hepatoma 3924 A and of a mammary tumour Biochim Biophys Acta *245* 263 1971
8 Zall D M Fisher D & Garner M Q Photometric determination of chlorides in water Anal Chem *28* 1665 1956

Submitted for publication October 26 1977

Achille Cittadini M D
Institute of General Pathology
School of Medicine
Via Pineta Sacchetti 644
00168 Rome
Italy

ANNOUNCEMENT

Teach in for consultants will be held at Queen Charlotte s Maternity Hospital November 26-30 1979

Topics

Ultrasound
- Prenatal diagnosis
- Medical complications of pregnancy
- Induction of labor
- Management of labor
- Neonatology

Male infertility
- Induction of ovulation

Extra corporeal fertilisation
Gynecological endocrinology
Hirsutism

Further information may be obtained from
Symposium Secretary
Institute of Obstetrics and Gynecology
Queen Charlotte s Maternity Hospital
Goldhawk Road
London W6 OXG
England

The 22nd British Congress of Obstetrics and Gynaecology will be held in Edinburgh from 8th 11th July 1980
For further information apply to
Congress Office
oyal College of Obstetricians & Gynaecologists
ssex Pla e
s Park
NW1 4RG
and

The Twenty first Postgraduate Institute for Pathologists in Clinical Cytopathology is to be given at The Johns Hopkins University School of Medicine and The Johns Hopkins Hospital Baltimore Maryland April 14-25 1980

The full two week program is designed for Pathologists who are Certified (or qualified) by the American Board of Pathology (PA) or their international equivalents

Information
John K Frost M D
610 Pathology Building
The Johns Hopkins Hospital
Baltimore Maryland 21205
USA

Application is to be made before March 7 1980

Official language English

IX Meeting of the International Study Group for Steroid Hormones will be held in Rome December 1979

Topics

Endocrinological cancer
breast cancer
prostate cancer
Ovarian function and disease

Further information may be obtained from
Professor Carlo Conti
International Study Group for Steroid Hormones
Clinica Medica V Policlinico Umberto I Università di Roma
Roma
Italy

Acta Obstet Gynecol Scand 58 401 – 403 1979

AMOXYCILLIN ABSORPTION AND PENETRATION IN PELVIC INFLAMMATORY DISEASE

Mathias Onsrud Halvard Gjonnæss and Tom Bergan

From the Department of Obstetrics and Gynecology and the Department of Microbiology Aker Hospital Oslo Norway

Abstract Five patients with pelvic inflammatory disease (PID) had thin polyethylene catheters introduced percutaneously through the abdominal wall into the pouch of Douglas for sampling of peritoneal fluid At hourly intervals specimens were aspirated simultaneously with the sampling of finger tip capillary blood In both the concentration of amoxycillin was determined by the micromethod of Jalling *et al* (1972) One hour after the oral ingestion of 0 5 grams of amoxycillin a therapeutic level was recorded in blood plasma the peak level being achieved in 2 hours The concentration of amoxycillin in the peritoneal fluid showed some delay mainly in the cases with a thick purulent exsudate but the peak levels were similar to those in blood plasma After a single dose of 0 5 gram of amoxycillin a therapeutic level was maintained in blood and in peritoneal fluid for 7 8 hours The drug was well tolerated and showed and excellent clinical effect

Amoxycillin is a semisynthetic penicillin which differs in chemical structure from ampicillin only in having a hydroxy group in para position on the benzene ring As to antibacterial activity the two antibiotics are similar However amoxycillin is absorbed more rapidly and gives higher serum levels than equimolar oral doses of ampicillin (7) There are indications that amoxycillin maintaines its penetration potential also to extra vascular compartments of the body since it produces higher levels in bronchial secretion than ampicillin when the serum concentrations are similar (4 8) A better bioavailability of amoxycillin is associated with smaller portions remaining unabsorbed in the intestinal contents so that a lower frequency of diarrhea results with amoxycillin than with ampicillin (9)

Ampicillin has been used extensively in pelvic inflammatory disease (PID) As recent reports indicated a favorable response to amoxycillin treatment (1) it seemed of interest to study the penetration of amoxycillin to the female pelvic organs in patients with PID The general pharmacokinetics of amoxycillin have been studied to date in healthy volunteers so that it was also of interest to see whether febrile illness would influence the uptake and elimination of the drug

Accordingly it was the aim of this study to determine the concentration of amoxycillin in plasma and in fluid from the Fallopian tubes after a single oral dose

MATERIAL AND METHODS

Subjects The five patients participating voluntarily in the study ranged from 16 to 23 years of age and weighed from 51 to 66 kg Their PID was verified by laparoscopy The cases were classified as *severe* or *mild* according to visual degree of inflammatory change whether the peritoneal fluid was purulent or serous and the erythrocyte sedimentation rate (ESR)

Particulars of the subjects were as follows

Case 1 ESR 44 mm/h purulent peritoneal fluid extensive inflammatory changes of the pelvis including a marked fibrinous exudate on the liver surface (Fitz Hugh Curtis syndrome)

Case 2 ESR 90 mm/h purulent peritoneal fluid

Case 3 4 5 ESR of 6 33 and 22 mm/h respectively all with serous peritoneal fluid

Dosage Eighteen to 20 hours after laparoscopy (*vide infra*) and after at least 8 hours of fasting a tablet of 0 5 g amoxycillin (Imacillin[R] Astra) was given with a mouthful of water The first dose was studied No other antimicrobial drug was given concomitantly A light breakfast was allowed after 1 hour

Sampling

Plasma Capillary blood was obtained from finger tip stab and collected in a hematocrite capillary tube

Peritoneal fluid Under visual guidance through a laparoscope a thin polyethylene catheter was introduced percutaneously through the abdominal wall to the pouch of Douglas to enable sampling of the peritoneal fluid collecting there At each sampling 0 5 1 0 ml of the fluid was aspirated through the catheter To ensure that the sample represented the fluid present in fossa Douglasi at the time of collection the catheter was emptied by insufflation of small quantities of air both immediately before and promptly after each sampling The catheter was removed after completion of the study

The patients were supine during the study

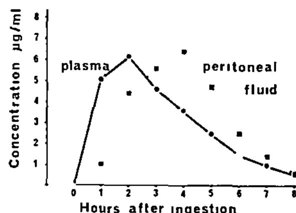


Fig 1 Mean plasma and peritoneal fluid concentration in five cases of pelvic inflammatory disease receiving a single dose of 0 5 gram amoxycillin perorally

Antibiotic assay The amoxycillin was assayed by the method of Jalling *et al* (3) Both serum and peritoneal fluid were assayed against standard discs produced by AB Biodisk The samples were assayed immediately without prior storage

RESULTS

Plasma concentrations A mean peak plasma concentration of 6 µg/ml was obtained two hours after in tion of 0 5 gram of amoxycillin (Fig 1) This was wed by a gradual decline so that detectable nts of amoxycillin were still present after 8 rs There was some variation in the maximum concentrations and in the intervals before these were achieved (Fig 2) This however could not be related to the severity of the disease

Peritoneal fluid concentration In peritoneal fluid the mean peak concentration of amoxycillin was recorded 4 hours after the ingestion i e 2 hours after the corresponding plasma peak (Fig 1) The peak levels and the areas under the curves were similar for peritoneal fluid and plasma The delay for the peritoneal fluid curve varied from 0 to 3 hours being most pronounced in the 2 cases classified as severe PID with frank purulent pelvic aspirates In the 3 cases of mild PID the blood and peritoneal fluid concentrations followed each other more closely (Fig 2)

Clinical effect The treatment with amoxycillin 0 5 gram three times daily continued for 10-18 days None of the five patients experienced side effects and all were obviously cured by the drug

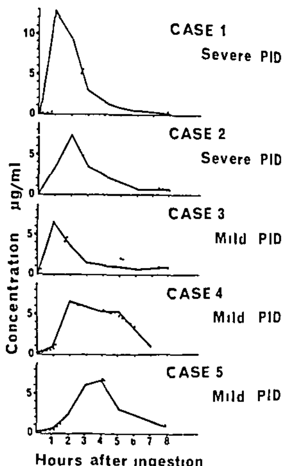


Fig 2 Individual concentration curves for the five patients studied Plasma concentration — peritoneal fluid concentration All cases got 0 5 gram amoxycillin per os at time 0

DISCUSSION

The penetration of antibiotics to the actual site of infection is clearly of crucial importance Endosalpingitis is undoubtedly a primary lesion in PID so that the clinical effect of a drug will depend on the concentration in the tubal fluid together with the drug s antibiotic effect In a previous study of doxycillin penetration (2) the drug concentration was practically identical in tubal and peritoneal fluid even in cases of tubal occlusion In the present study all the patient had patent Fallopian tubes We therefore presume the peritoneal fluid of the pouch of Douglas to be representative for the tubal fluid

For most of the actual microbes in PID the *in vitro* minimum inhibitory concentration of amoxycillin is 1 µg/ml (6) Our study shows that after oral administration of 0 5 g of amoxycillin a therapeutic level is

maintained for 7 8 hours in plasma and peritoneal fluid The modest delay for drug penetration in some of the cases is probably of minor clinical importance as indicated by the excellent clinical effect In view of the high amoxycillin concentrations that were achieved in the peritoneal fluid this drug should probably be effective also in more widespread intraperitoneal infections as for instance PID complicated by perihepatitis (Fitz Hugh Curtis syndrome) This syndrome is found in about 13 per cent of PID cases treated in our department (6)

ACKNOWLEDGEMENT

We are indebted to Mrs M Vangdal for technical assistance in performing the assays

REFERENCES

1 Furuya H Matsuda S Mori S Tanno M & Kobayasi T Clinical application of amoxycillin in the field of obstetrics and gynecology Chemotherapy (Tokyo) *21* 1752 1973
2 Gjønnæss H & Holten E Doxycillin (Vibramycin[R]) in pelvic inflammatory disease Acta Obstet Gynecol Scand (in press)
3 Jalling B Malmborg A S Lindman A & Borens L O Evaulation of a micromethod for determination of antibiotic concentration in plasma Eur J Clin Pharmacol *4* 150 1972
4 May J R & Ingold A Amoxycillin in the treatment of infections of the lower respiratory tract J Infect Dis Suppl *129* 189 1974
5 Murakawa T Yokota Y & Kono Y Amoxycillin its absorption excretion and metabolism after oral administration Chemotherapy *21* 1399 1973
6 Onsrud M Perihepatitis in pelvic inflammatory disease Association to intrauterine contraception (Submitted for publication)
7 Sutherland R Croydon E A P & Robinson G N Amoxycillin A new semisynthetic penicillin Br Med J *3* 13 1972
8 Tan G S Bannister T & Phair J P Level of amoxycillin in human serum and interstitial fluid J Infect Dis Suppl *129* 146 1974
9 Wise P J & Neu H C Experience with amoxycillin An overall summary of clinical trials in United States J Infect Dis Suppl *129* 266 1974

Submitted for publication March 29 1978

Mathias Onsrud M D
Tisue Typing Laboratory
Rikshospitalet
Oslo
Norway

ANNOUNCEMENT

In the beginning of October this year the 17th volume of the *Annual Report on the Results of Treatment in Gynecological Cancer* will appear It is published by the Cancer Committee of the International Federation of Gynecology and Obstetrics

The first *Annual Report* was published in 1937 The seven latest volumes have appeared at three yearly intervals In 1958 FIGO assumed the patronage of the *Annual Report* The work is sponsored by cancer societies and gynecological societies and by the WHO The value of the *Annual Report* for scientific studies in carcinoma of the female pelvis has been stressed by many organizations

The aim of the work is to establish international agreement on classification clinical staging pathology and presentation of end results in cases of carcinoma in the female pelvis

In the 17th *Annual Report* 105 institutions from 28 countries are collaborating 100 institutions report on 38 461 cases of invasive carcinoma of the cervix, 70 institutions report on 10 720 cases of carcinoma of the corpus and 57 institutions report on 6 287 cases on ovarian tumors examined and treated in the years 1969 1972 In addition data on 2 983 cases of invasive carcinoma of the vulva examined in the years 1963 1972 and submitted by 61 institutions are presented Thus for the first time the *Annual Report* speaks for all the major aspects of gynecological malignant disease Information is given concerning stage distribution age of patient histology treatment applied and 5 year survival The individual institutions are presented in 17 tables Eleven graphs illustrate the entire material within each site

Volume 17 of the *Annual Report* can be purchased from the

Editorial Office of the *Annual Report*
Radiumhemmet
S 104 01 Stockholm
Sweden

The price is U S dollars 15

Acta Obstet Gynecol Scand 58 405–408 1979

RECURRENCES AND METASTASES IN CARCINOMA OF THE UTERINE BODY CORRELATED TO THE SIZE AND LOCALIZATION OF THE PRIMARY TUMOR

J E Johnsson

From the Gynecological Section Department of Oncology University of Lund Lund Sweden

Abstract Hysterography was used for judging the size and location of the primary tumor in 475 patients with stage I carcinoma of the uterine body No increased frequency of recurrence and metastases was noted in patients where the tumor involved the uterine cervix Large tumors however were accompanied by an increased frequency of recurrences metastases in the pelvic nodes and remote metastases

Localization of the primary tumor in the corpus and the cervix in carcinoma of the uterine body has been the subject of much interest Tumors involving the cervix have as a rule been thought to require more aggressive treatment than those confined to the uterine body (4 5 6 10 12) Certain reports however question the validity of this assertion (14 15 18 21)

This article examines the relation between recurrences and metastases and the size and location of the primary tumor as judged hysterographically

MATERIAL AND METHODS

The material consists of 490 patients with carcinoma of the uterine body stage I primarily treated at the Gynecological Section of the Department of Oncology between 1951 and 1960 Staging was performed according to FIGO-classification using curettage and gynecological examination (12)

The patients were investigated by hysterography 2 5 weeks after the primary curettage the day before the first intracavitary radium treatment The hysterograms were examined to find whether

a the tumor was confined to the uterine body
b it also involved the upper third of the cervix
c it also involved more than the upper third of the cervix and
d to estimate the size of the tumor in the uterine body i e
I growth involving at the most one third of the endometrium or
II growth involving more than one third of the endometrium (Fig 1)

Judge in tis way the localization of the tumor in the corpus cervix and the size of the tumor in corpus was determined in 475 of the patients

Therapy consisted of two treatments with intracavitary radium at an interval of three weeks using Heyman s packing method This was followed by total abdominal hysterectomy and bilateral salpingo oophorectomy 6-8 weeks after the end of radium treatment except in cases where this was contra indicated by the patient s general condition

Recurrences and metastases were recorded for five years following the start of treatment

Remote metastases included deposits in the lungs and pleurae skeleton cerebrum liver and supraclavicular fossae

RESULTS

Tables I and II show metastases which were either discovered during hysterectomy or at follow up after the conclusion of treatment

Tables III and IV show the frequency of metastases in the upper and lower halves of the vagina respectively according to the use of radiotherapy alone or when combined with hysterectomy As the numbers of cases are rather small no attempt has been made to relate the occurrence of vaginal metastases to the

Table I *Metastases on the pelvic walls and remote metastases in relation to tumor localization*

Localization	Metastases on the pelvic walls	Remote metastases
Corpus	6/278 (2%)	28/278 (10%)
Corpus and upper third of the cervix	6/151 (4%)	16/151 (11%)
Corpus and more than upper third of the cervix	1/46 (~2%)	2/46 (~4%)
Total	13/475 (3%)	46/475 (10%)

Table II *Metastases on the pelvic walls and remote metastases in relation to size of tumor*

Size of tumor	Metastases on the pelvic walls	Remote metastases
≤One third of the endometrium	0/117 (0%)	3/117 (3%)
>One third of the endomtrium	13/358 (4%)	43/358 12%)
Total	13/475 (3%)	46/475 (10%)

Table III *Vaginal metastases in relation to tumor localization*

Localization	Radiotherapy alone Upper vag	Radiotherapy alone Lower vag	Radiotherapy and hysterectomy Upper vag	Radiotherapy and hysterectomy Lower vag
Corpus	4/124 (3%)	2/124 (2%)	5/154 (3%)	1/154 (1%)
Corpus and cervix	2/92 (2%)	1/92 (1%)	1/105 (1%)	0/105 (0%)
Total	6/216 (3%)	3/216 (1%)	6/259 (2%)	1/259 (1%)

extent of invasion of the cervix No metastases however were observed when the tumor involved more than the upper third of the cervix

Tumor recurrence in 216 women receiving radiotherapy alone and adnexal metastases or the presence of metastases in pelvic peritoneum of 259 women having radiotherapy and surgery was studied in relation to the extent of the uterine tumor

DISCUSSION

Determination of tumor localization and tumor size in patients with cancer of the uterine body has previously been done solely by gynecological examination and fractional curettage The significance of involvement of the cervix had aroused discussion but the size of the tumor mass has not been the subject of much research

The use of a currette to determine the size and ocalization of a tumor in the cavity of the uterus and cervical canal cannot be precise even for the physician The results obtained by iod have been difficult to assess (20 24) are however two methods of investigation in routine clinical use which allow more accurate determination of the localization and size of tumors These are hysterography and hysteroscopy (7 8 9 16 17 22 25) The present investigation has employed hysterography for this purpose The spread of tumor to the cervix has been assumed in most reports to give a poorer prognosis due to spread to the nearby pelvic lymph nodes Some investigators have questioned the association of a poorer prognosis with cervical involvement (14 15 18 21) and when hysterography for localization of the tumor has been used no definite evidence for poorer prognosis has been observed in such cases (9)

When the lymph flow from the corpus and the cervix is considered cervical involvement seems unlikely to increase the difficulty of treatment (Fig 2) (19) The regional lymph nodes for most of the uterine body are para aortic There is overlap between the areas draining to the different groups of nodes Tumors localized in the lower part of the corpus or involving the cervix drain to the pelvic nodes and ought to have a better prognosis than tumors localized to the fundus as the para aortic nodes are very difficult either to irradiate adequately or to remove surgically Pelvic lymphadenoectomy or irradiation are technically easier to perform

Tumors growing superficially on the portio-cervix (stages 0 IA) very seldom metastasize to the regional lymph nodes irregardless of whether they consist of squamous cell cancer or of adenocarcinoma It is therefore unlikely that the localization of the tumor in the corpus cervix has any decisive influence on the frequency of metastases No increased frequency of metastases on the pelvic walls was noted in this study when the tumor involved the cervix The incidence of lymph node metastases was low and agreed well with the frequency of metastases found where no lymphadenoectomy was done with hysterectomy (1 11

Table IV *Vaginal metastases in relation to the size of tumor*

Size of tumor	Radiotherapy alone Upper vag	Radiotherapy alone Lower vag	Radiotherapy and hysterectomy Upper vag	Radiotherapy and hysterectomy Lower vag
≤One third of the endometrium	1/50 (~2%)	0/50 (~0%)	1/67 (~2%)	0/67 (~0%)
>One third of the endometrium	5/166 (3%)	3/166 (2%)	5/192 (3%)	1/192 (1%)
Total	6/216 (3%)	3/216 (1%)	6/259 (2%)	1/259 (1%)

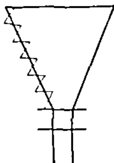


Fig 1 Diagram of frontal plane of the uterus with growth involving one third of the endometrium

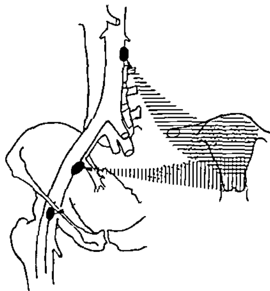


Fig 2 Regional lymph node stations of the uterus

23) Treatment-centers which use routine lym phadenectomy at surgery report a frequency of in volvement of about 15 per cent (3 13)

The way in which the size of the tumorous mass in fluences the frequency of metastases in the regional lymph nodes has been investigated by Creasman *et al* (1976) (2) in a study in which lymphadenectomy was part of surgical treatment Of patients in whom the size of the uterus was at most 8 cm measured by vaginal sound 6 2 per cent had metastases in the pelvic nodes and 3 8 per cent in the para aortic nodes while the corresponding figures in patients with a uterus measuring more than 8 cm were 18 per cent and 11 7 per cent respectively The same tendency was found in the present study When the size of the tumor was hysterographically judged as small i e about one third of the surface of the endometrium no metastases were demonstrated When there was large tumorous mass 4 per cent had metastases in the pelvic nodes

The frequency of remote metastases was lower with small tumorous mass (3 per cent) than when it was large (12 per cent)

The number of vaginal metastases and metastases *in the ovaries in this investigation was small but there* was a tendency to higher rates in patients with large tumours There were however too few observations to allow any proper evaluation

The frequency of recurrence among patients treated solely with radiation was not dependent on tumorlocalization Large tumourmasses on the other hand showed a higher rate of recurrence This should not however be interpreted only as a sign of ag gressive tumor infiltrating deeply in the myometrium as it is partly due to the difficulties of giving a satisfactory irradiation to the entire tumor using in tracavitary technique when the tumor is large and especially when it is growing exophytically

CONCLUSION

Localization of a tumor in the corpus-cervix es-tablished by hysterography was associated with no change in the frequency of recurrences and metasta ses Large tumors on the other hand regardless of

Table V *Recurrences and adnexal metastases in relation to the localization of tumor*

Localization	Radiotherapy Recurrences	Radiotherapy and surgery Adnexal metastases
Corpus	28/124 (23%)	10/154 (7%)
Corpus and upper third of the cervix	20/68 (29%)	2/83 (2%)
Corpus and more than upper third of the cervix	6/24	1/22
Total	54/216 (25%)	13/259 (5%)

Table VI *Recurrences and metastases in relation to the size of tumor*

Size of tumor	Radiotherapy Recurrences	Radiotherapy and surgery Adnexal metastases
≤One third of the endometrium	5/50 (−10∞)	2/67 (−3%)
>One third of the endometrium	49/166 (30%)	11/192 (6%)
Total	54/216 (25%)	13/259 (5%)

their localization gave a higher frequency of recurrences metastases on the pelvic walls and remote metastases This information is of value in planning treatment Aggressive treatment implying an increased frequency of complications can be reserved for patients whose tumors are likely to have spread beyond the uterus

REFERENCES

1 Boronow R C Carcinoma of the corpus Treatment at M D Anderson Hospital Cancer of the uterus and ovary Year Book Medical Publ Chicago 1969
2 Creasman W T Boronow R C Morrow C P Disaia P J & Blessing J Adenocarcinoma of the endometrium its metastatic lymph node potential A preliminary report Gynecol Oncol *4* 239 1976
3 Davis W Carcinoma of the corups uteri A study of 525 cases at the New York Hospital (1932 1961) Am J Obstet Gynecol *88* 163 1964
4 Delclos L & Fletcher G H Malignant tumors of the endometrium Evaluation of some aspects of radiotherapy Cancer of the uterus and ovary Year Medical Publ Chicago 1969
ley H D Boronow R C & Lewis J L Stage endometrial adenocarcinoma Memorial Hospital for Cancer 1949 1965 Obstet and Gynecol *49* 604 1977
6 Joelsson I Sandri A & Kottmeier H L Carcinoma of the uterine corpus A retrospective survey of individualized therapy Acta Radiol (Suppl) (Stockholm) 334 1973
7 Joelsson I Levine R U & Moberger G Hysteroscopy as an adjunct in determining the extent of carcinoma of the endometrium Am J Obstet Gynecol *11* 696 1971
8 Johnsson J E Hysterography and diagnostic curettage in carcinoma of the uterine body An evaluation of diagnostic value and therapeutic implication in stages I and II Acta radiol (Suppl) (Stockholm) 326 1973
9 Johnsson J E & Norman O Relation between prognosis in early carcinoma of the uterine body and hysterographically assessed localization and size of tumour In press
10 Kjellgren O & Magnusson S S Efficacy of primary radiation in carcinoma of the endometrium Acta Radiol (Ther) (Stockholm) *9* 102 1970
11 Kottmeier H L Carcinoma of the corpus Its classification and treatment Gynecol *138* 287 1954
12 Kottmeier H L Annual report on the results of treatment of carcinoma of the uterus and vagina Vol XIII Norstedts Stockholm 1964
13 Lees D H An evaluation of treatment in carcinoma of the body of the uterus Br J Obstet Gynecol *76* 615 1969
14 Lefèvre H Node dissection in cancer of the endometrium Surg Gynecol Obstet *107* 649, 1956
15 Lindgren M The prognosis of carcinoma of the endometrium in its different stages treated by surgery combined with postoperative radiotherapy Acta Obstet Gynecol Scand *36* 426 1957
16 Norman O Hysterography in cancer of the corpus of the uterus Acta Radiol (Suppl) (Stockholm) 79 1950
17 Norman O Hysterography in cancer of the corpus of the uterus Acta Radiol (Suppl) (Stockholm) 79 1950
18 Plentl A A & Friedman E A Lymphatic system of the female genitalia The morphologic basis of oncologic diagnosis and therapy W B Saunders Co Philadelphia 1971
19 Reiffenstuhl G The lymphatics of the female genital organs Lippincott Philadelphia 1964
20 Roberts D W T Carcinoma of the body of the uterus at Chelsea Hospital for Women 1943 1953 Br J Obstet Gynecol *68* 132 1961
21 Schwartz A E & Brunschwig A Radical panhysterectomy and pelvic node excision for carcinoma of the corpus uteri Surg Gynecol Obstet *105* 675 1957
22 Tak W K Anderson B Vardi J R Beecham J B & Marchant D J Myometrial invasion and hysterography in endometrial carcinoma Obstet and Gynecol *50* 159 1977
23 Willmott Dobbie B M Taylor C W & Waterhouse J A H A study of carcinoma of the endometrium Br J Obstet Gynecol *72* 659 1965
24 Winterton W R Discussion on carcinoma of the body of the uterus Proc Roy Soc Med *57* 10 1964
25 Wolff J P Goldfarb E Rumeau Rouquette Cl & Breart G The value of hysterogram for the prognosis of endometrial cancer Gynecol Oncol *3* 103 1975

Submitted for publication February 1 1978

J E Johnsson
Gynecological Section
Department of Oncology
University of Lund
S 221 85 Lund
Sweden

Acta Obstet Gynecol Scand 58 409–410 1979

SHORT COMMUNICATION

FETOSCOPY

Björn Gustavii Eric Cordesius Lars Löfberg and Per Strömberg

From the Department of Obstetrics and Gynecology
University Hospital Lund Sweden

Abstract A brief report is given on fetal blood sampling by fetoscopy in three fetuses at risk for severe congenital bleeding disorder hemophilia A in two cases von Willebrand s disease in one Published reports on complications of fetoscopy are reviewed Out of all together about one hundred pregnancies that have been allowed to continue after fetoscopy five ended in miscarriage No other serious complication has been reported

It is now possible to penetrate the amniotic cavity with an endoscope and to obtain a sample of fetal blood from a vessel on the surface of the placenta under direct visual control Such sampling is done under local anesthesia and is usually performed in the 18th to 20th week of pregnancy

After three years experience with fetoscopy at elective abortions we started fetoscopy for the purpose of prenatal diagnosis Three of the cases in this series of diagnostic fetoscopy are relevant to the subject of this meeting and they are reviewed below

Case reports Two of the fetuses examined were at risk for classic hemophilia (hemophilia A) The first one had a low concentration of factor VIII This value and the diagnosis of severe hemophilia were confirmed with blood from the abortus after termination of the pregnancy The other fetus had a normal concentration of factor VIII and the mother continued the pregnancy To date 10 weeks after the fetoscopy the pregnancy is continuing normally In a third fetus von Willebrand s disease was excluded (5) The pregnancy was carried to term and the infant had a normal concentration of the von Willebrand s factor at birth All samples were analyzed by an immunoradiometric technique (8) Fetuses at risk for classic hemophilia have been examined in the same way at Yale University (2) and at King s College Hospital Medical School London (9)

Risks at fetoscopy Judging from the literature about one hundred pregnancies have been allowed to continue after fetoscopy (Included are besides the cases of fetal blood sampling also those cases where the fetoscopy was done to reveal any external malformations of the fetus) Of these about one hundred pregnancies five ended in miscarriage (1 2 3 6)

One miscarriage occurred 10 weeks after fetoscopy which was done in the 16th week of pregnancy The aborted fetus was macerated and its gestational age was estimated to be 16 to 18 weeks The placenta was located anteriorly and it was thought that the fetoscope had injured the margin of the placenta resulting in bleeding and thereby fetal death

Another woman aborted also 10 weeks after fetoscopy and judging from the size of the fetus the time of death coincided with that of fetoscopy Though fetoscopy had presumably caused the death it was not possible to find out exactly how

In a third case ultrasound examination 9 hours after fetoscopy showed that the fetus was dead Abortion was induced Examination of the fetus and the placenta did not reveal any injury But the amniotic fluid was bloody and judging from the cell count the fetus had lost at least 5 milliliters of blood At this age 18 weeks a fetus normally has 40 milliliters of blood

In the fourth case rupture of the fetal membranes occurred 2 days after fetoscopy and 2 days later the fetus was delivered

As for the fifth miscarriage no details were given

Three women had leakage of amniotic fluid from the vagina (4 7) All had normal babies One of them was delivered five weeks before term the other two at term

There is no report on fetal injury caused by the fetoscope

other cases (no 2 6 9) no significant change in migration was observed and only in one case (no 1) the migration area was increased in the presence of paternal serum The results are presented in Table I

DISCUSSION

The results suggest that maternal lymphocytes sensitised *in vivo* to fetal antigens which are partly of paternal origin may produce a migration inhibition factor when reexposed *in vitro* to some of these antigens The activity of the migration inhibition factor seems to be suppressed in the presence of maternal serum This inhibitory effect similar to the blocking effect of maternal serum on mixed leukocyte culture (7) may be due to non immunological factors like pregnancy associated alpha$_2$-glycoproteins (11) hormonal factors It is also possible that an immunological mechanism is involved in this suppressive effect The neutralization of specifically activated lymphocyte mediators by maternal serum may be one of the possible protective mechanisms of maternal humoral factors in the fetal maternal relationship

REFERENCES

1 Halbrecht I & Komlos L Lymphocyte transformation in mixed wife husband leukocyte cultures in abor[illegible] and in hydatidiform moles Obstet Gynecol [illegible] 1968
2 [illegible]t I & Komlos L Lymphocyte transforma[illegible] in wife husband mixed leukocyte cultures in normal and pathological pregnancies *In* Current Problems in Fertility (ed A Ingelman Sundberg and N O Lunell) p 215 Plenum Press London 1971
3 Halbrecht I & Komlos L Mixed wife-husband leukocyte cultures in disturbed and pathological pregnancies Further studies Isr J Med Sci *10* 1100 1974
4 Jenkins D M & Hancock K W Maternal unresponsiveness to paternal histocompatibility antigens in human pregnancy Transplantation *13* 618 1972
5 Jones E & Curzen P Blocking one way maternal foetal MLR Nature New Biol *250* 791 1974
6 Kasakura S A factor in maternal plasma during pregnancy that suppresses the reactivity of mixed leukocyte cultures J Immunol *107* 1296 1971
7 Leventhal B G Buell D N Jankee R Rogentine G N Jr & Terasaki P The mixed leukocyte response effect of maternal plasma *In* Proceedings of the Fifth Leukocyte Culture Conference (ed J E Harris) p 473 Academic Press New York 1970
8 Lewis J Whang J Nagel B Oppenheim J J & Perry S Lymphocyte transformation test in mixed leukocyte cultures in women with normal pregnancy and tumors of placental origin Am J Obstet Gynecol *96* 287 1966
9 Ohama K & Kadotani T Lymphocyte reaction in mixed wife husband leukocyte cultures in relation to infertility Am J Obstet Gynecol *109* 477 1971
10 Soborg M & Bendixen C Human lymphocyte migration as a parameter of hypersensitivity Acta Med Scand *181* 247 1967
11 Stimson W H Immunosuppressive effect of pregnancy associated alpha macroglobulin Lancet *ii* 989 1975
12 Youtananukorn V & Matangkasombut P Specific plasma factors blocking human maternal cell mediated immune reaction to placental antigens Nature New Biol *242* 110 1973

Submitted for publication March 28 1978

I Halbrecht M D
Gattegno Research Institute of Human Reproduction and Fetal Development
Hasharon Hospital
Petah Tiqva
Israel

Acta Obstet Gynecol Scand 58 413–414 1979

SHORT COMMUNICATION

NEUTRALIZING ANTIBODIES AGAINST HERPES SIMPLEX VIRUS IN MATERNAL AND UMBILICAL CORD SERUM

Tatsuya Ishiguro and Yoshikatsu Ozaki

From the Department of Obstetrics and Gynecology Kansai Medical University Osakaand the Department of Microbiology Shiga University of Medical Science Shiga Japan

Abstract Thirteen Japanese with a full term pregnancy were studied to determine maternal and neonatal serum neutralizing antibodies against herpe simplex virus (HSV) The study included 10 healthy persons 2 with herpes genitalis and one with herpes oralis We found that the serum neutralizing antibody titers in neonates were almost identical or slightly higher as compared to those in the mother and such findings suggest that in the neonate the la k of certain immunological responses may be responsible for generalized herpes simplex virus infection

During the past decade numerous studies have demonstrated the association between herpes simplex virus (HSV) and cervical cancer Less attention has been given to herpetic infection in pregnancy yet such an infection present at the time of labor may result in neonatal death (1 4 6) It is generally agreed that Cesarean section is the best approach in order to avoid the risks to the newborn child However whether or not the neonate has an immunological capacity to ward off herpetic infection has not been demonstrated The present study was designed to determine the serum neutralizing antibodies against HSV in neonates

MATERIAL AND METHODS

Serum samples Thirteen Japanese women with a full term pregnancy were studied Included were ten healthy women two with herpes genitalis and one with herpes oralis These herpes manifestations were confirmed by viral culture or exfoliative cytological examination and both patients with herpes genitalis underwent a Cesarean section Maternal blood was obtained during labor and blood was taken from

Table I *Maternal and neonatal antibodies against herpes simplex virus*

Case	Maternal age	Para	Serum neutralizing antibody titers HSV – I Mother	HSV – I Neonate	HSV – II Mother	HSV – II Neonate	II/I index Mother	II/I index Neonate
Healthy mother								
1	26	p	2 50	? 65	1 75	1 83	70 0	69 1
2	25	p	1 75	1 90	1 30	1 45	74 3	76 3
3	27	m	1 75	1 75	1 45	1 60	82 9	91 4
4	28	m	1 75	1 75	1 53	1 45	87 4	82 9
5	31	p	1 45	1 53	1 30	1 23	89 7	80 4
6	23	p	1 00	1 15	1 23	1 30	123 0	113 0
7	22	p	0	0	0	0	—	—
8	22	p	0	0	0	0	—	—
9	?6	p	0	0	0	0	—	—
10	27	m	0	0	0	0	—	—
Mother with herpetic lesion								
1†	28	p	0	0	0	0	—	—
2†	33	p	0	0	0	0	—	—
3	5	p	1 15	1 15	0	0	—	—

1† † Herpes ge ital s 3 Herpes oralis
Abbreviation p primipara m multipara

umbilical cord immediately after delivery respectively Sera were stored at 20 C until assay and the 26 serum samples were examined simultaneously
Titration of neutralizing antibodies This was done by the microneutralization method described previously (3 5)

RESULTS AND DISCUSSION

Both maternal and neonatal neutralizing antibody titers are shown in Table I The antibodies were absent in the neonate delivered from the mother who had no antibodies while such were present in the neonate from the mother with antibodies and the levels were almost identical or slightly higher as compared to those in maternal sera

The incidence of disseminated herpetic infection is high in infants vaginally delivered from mothers with herpes genitalis (1 4 6) Generalized HSV infection is regarded as exceedingly rare in adults with circulating neutralizing antibodies and is retstricted to those with burns alcoholics or those undergoing immunosuppressive chemotherapy (2) Humoral antibodies apparently prevent general dissemination of the virus in healthy adults although recurrence is not uncommon in HSV infection Nahmias and co workers (4) reported six neonates with disseminated herpetic infection two of whom had transplacental antibodies The amount of antibodies present in these neonates was not reported It is apparent from our present ngs however that a significant amount of anti has been transferred to neonates who are de from mothers with antibodies and that these e sufficiently adequate to prevent dissemi ted infection in adults Accordingly it is speculated that in neonates the lack of certain immuno response(s) other than neutralizing antibodies such as cellular immunity may be responsible for generalized HSV infection

ACKNOWLEDGEMENTS

Thanks are due to Professor I Sawaragi Department of Obstetrics and Gynecology Kansai Medical University for pertinent discussion and to M Ohara Kyoto University for advice on the manuscript

REFERENCES

1 Amstey M S & Monif G R G Genital herpesvirus infection in pregnancy Obstet Gynecol *44* 394 1974
2 Ishiguro T Matsunami M Funakoshi S Yasuda M Ozaki Y & Kotani S Cytologic and virologic studies of herpetic pneumonia J Am Med Women Assoc *33* 124 1978
3 Ishiguro T & Ozaki Y Sexual behavior and antibodies to herpes simplex virus in healthy Japanese women J Am Med Women Assoc *33* 271 1978
4 Nahmias A J Josey W E Naib Z M Freeman M G Fernandez R J & Wheeler J H Perinatal risk associated with maternal genital herpes simplex virus infection Am J Obstet Gynecol *110* 825 1971
5 Ozaki Y Ishiguro T Ohashi M Sawaragi I & Ito Y Antibodies to herpesvirus type 1 and type 2 among Japanese cervical cancer patients Gann *69* 119 1978
6 Vesterinen E Savolainen E R Purola E Saksela E & Leinikki P Occurrence of genital herpes simplex and cytomegalovirus infections in pregnancy Acta Obstet Gynecol Scand *56* 101 1977

Submitted for publication February 6 1978

Tatsuya Ishiguro M D
Department of Obstetrics and Gynecology
Kansai Medical University
Moriguchi
Osaka 570
Japan

Acta Obstet Gynecol Scand 58 415–416 1979

CASE REPORT

ARTERIOGRAPHY AND CHEMOTHERAPY IN LOCALIZED TROPHOBLASTIC DISEASE BY MEANS OF LOCAL (PELVIC) INTRAARTERIAL INFUSION

Jack A Goldman Dan Peleg Moshe Agmon and Gerald Shapiro

From the Department of Obstetrics and Gynecology Hasharon Hospital and the Sackler School of Medicine Tel Aviv University Tel Aviv Israel

Abstract In spite of considerable progress in systemic chemotherapy in malignant throphoblastic disease there remains a small group of patients who fail to respond to this type of therapy Here the trophoblastic process may be localized by means of an arteriography and treated by a local intraarterial infusion of cytotoxic compounds in high concentration The latter makes possible the treatment of processes localized in essential organs which are hard to remove as well as in young women wishing to preserve their reproductive capacity

Our experience is limited to one case of a young woman with chorioadenoma destruens in the uterus resistant to systemic chemotherapy yet sucessfully treated with pelvic intraarterial infusion of cytotoxics

In the past decade great progress has been registered in the management of malignant trophoblastic disease by means of chemotherapy the drugs of choice being Methotrexate and Actinomycin D In fact the rate of general remissions achieved in non metastatic trophoblastic disease has been reported to be between 0-100 per cent (4 5) Nevertheless patients failing to respond to systemic chemotherapy pose two main problems to the clinician the precise localization of the trophoblastic process must be determined and the choice of the mode of therapy must be made

Our patient is an example of the contribution of arteriography to localize the process and its successful treatment by means of a pelvic intraarterial cytotoxic infusion

CASE REPORT

B A a 24-years-old married female gravida 0 para 0 was admitted to the Gynecological Department of Hasharon Hospital She had undergone a curettage for hydatidiform mole in another hospital In view of the fact that human chorioni gonadotrophin levels in the urine had remained elevated she recei ed repeated series of systemic therapy with Methotrexate and Actinomycin D A second curettage was done but only uterine muscle was obtained

On admission 4 months after discovery of the trophoblastic disease her general condition was fair General as well as pelvic examination revealed no unusual findings Scanning of the brain bones lungs and liver were negative Yet urinary chorionic gonadatropin values ranged between 2000-4000 international units We proceeded with another 3 consecutive series of Methotrexate (intramuscular 0 4 mg/kg/day) and Actinomycin D (intravenous 10 mcg/kg/day) over 5 days Nevertheless following this therapy hCG values as well as its β subunits remained elevated Arteriography (Seldinger method (7)) was done (see figure 1) since the patient expressed her wish to conserve her reproductive capacity laparotomy was performed with direct introduction of catheters into the hypogastric arteries by the method of Smith *et al* (10) for intraarterial infusion Examination of the pelvic organs revealed a slightly enlarged uterus with no obvious macroscopic pathology The adnexa were normal as well as the other internal organs in the abdominal cavity

By intraarterial infusion she received during one week a dose of 3 microgram/kg daily of Actinomycin D During the entire period of both systemic and local therapy liver function tests as well as repeat blood counts remained within normal limits

At the completion of local infusion values of the β subunits of hCG fell to very low levels and later reverted to normal

Following repeated negati e tests the patient was discharged It is interesting to note that in spite of the improvements in laboratory values repeat arteriography through the catheters in the hypogastric arteries revealed only a slight improvement over the previous examination

COMMENT

The characteristics of arteriography in malignant trophoblastic disease limited to the uterus have been described by Borell (1) and others (2 3 6 11 12) These are the emphasis of the uterine vessels and spotting of the growth in irregular cavities Nevertheless the abscence of these findings does not rule out the existence of malignant trophoblastic foci in the uterus (9) The route of therapy to be followed by



the clinician is either the resection of the uterus or local *intraarterial infusion of cytotoxic drugs The latter* conservative therapy must be applied in the young woman as was the case in this patient

The preferred way of introduction of catheters into the hypogastric vessels is by direct exposure at lapa otomy This procedure permits the direct inspection *e internal genital and abdominal organs* and the introduction of the catheters Furthermore the al artery route is not recommended because of *sible complications (8) Naturally* the success of the infusion depends on the continuous administration of heparin and antibiotics It may be noted that the only way to *monitor the treatment is the titration* and follow up of hCG and its β subunits Arteriography on the other hand can hardly be used to indicate the success of therapy as was *demonstrated in* our case

Nevertheless a review of the literature as well as this case re emphasize the value of arteriography and the local intraarterial infusion of cytostatics in the diagnosis and therapy of patients with trophoblastic disease limited to the uterus and resistant to systemic therapy such conservative therapy makes possible future pregnancies

Note Following amenorrhea of 8 months regular menses have now resumed

1 Borell U Fernström I & Westmen A Value of pelvic arteriography in diagnosis of mole and chorionepithelioma Acta Radiol *44* 378 1955
2 Brewis R A L & Bagshawe K D Pelvic arteriography in invasive trophoblastic neoplasia Brit J Radiol *41* 481 1968
3 Cockshott W P Evans K T & Hendrickse J P Arteriography of trophoblastic tumours Clin Radiol *15* 1 1954
4 Hammond C B & Parker R T Diagnosis and treatment of trophoblastic disease Obstet Gynecol *35* 13? 1970
5 Hammond C B Borchert L G Tyrey L Creasman W T & Parker R T Treatment of metastatic trophoblastic disease good and poor prognosis Am J Obstet Gynecol *115* 451 1973
6 Hendrickse J P Cockshott W P Evans K T & Barton C J Pelvic angiography in diagnosis of malignant trophoblastic disease New Eng J Med *271* 859 1964
7 Lewis J Gore H Hertig A T & Goss D A Treatment of trophoblastic disease Am J Obstet Gynecol *96* 710 1966
8 Marcoulis G B Hammond C B Johnsrude I S Weed J C & Parker R T Areteriography and infusional chemotherapy in localized trophoblastic disease Obstet Gynecol *45* 397 1975
9 Shimkin P M Van Thiel D H & Ross G T Selective hypogastric arteriography in uterine choriocarcinoma Am J Roentgenol Rad Ther Nucl Med *111* 535 1971
10 Smith J P Randall G E Castro J R & Lindberg R D Hypogastric artery infusion and radiation therapy for advanced squamous cell carcinoma of the cervix Am J Roentgen Rad Ther Nucl Med *114* 110 1972
11 Sullivan R D Miller E & Sykes M P Antimetabolite metabolite combination cancer chemotherapy effects of intraarterial methotrexate and intramuscular citrovorum factory therapy in human cancer Cancer *12* 1248 1959
12 Takahshi M & Nagata Y Angiography of trophoblastic tumors Am J Roentgenol *112* 779 1971

Submitted for publication January 1 1979

Jack A Goldman
Department of Obstetrics and Gynecology
Hasharon Hospital
Tel Aviv University Medical School
Petah Tikva
Israel

Acta Obstet Gynecol Scand 58 417–422 1979

THE IMMUNODEPRESSIVE EFFECT OF HUMAN GLUCOPROTEINS AND THEIR POSSIBLE ROLE IN THE NONREJECTION PROCESS DURING PREGNANCY

L Hammarström T Fuchs and C I E Smith

From the Department of Immunobiology Wallenberglaboratory Lilla Frescati Stockholm and the Department of Obstetrics and Gynecology Danderyd Hospital Danderyd Sweden

Abstract Human chorionic gonadotrophin (HCG) and human chorionic somatomammotrophin (HCS) were shown to suppress the proliferative T and B cell response induced by different mitogens in human and mouse lymphocytes Thyroid stimulating hormone (TSH) sharing the alpha chain subunit with HCG was devoid of effect suggesting that the immunosuppressive entity is localized within the beta chain subunit Human growth hormone (HGH) which is partly biologically cross reactive with HCS did not impair mitogen responsiveness

HCG was also able to inhibit the differentiation of cells since the induction of antibody formation was depressed Expression of plaque forming cells was also reduced by addition of HCG directly in the PFC assay possibly reflecting the anti-complementary effect of this hormone since cell mediated lysis of target cells by Con A activated lymphocytes which is not complement dependent was unaffected by adding HCG in the assay system

There is as yet no conclusive evidence as to why the fetus who expresses paternal transplantation antigens sucessfully can engraft into and remain in the uterus and although a vaste number of hypotheses have been proposed the mechanisms preventing the rejection of this histoincompatible graft are still poorly understood Earlier suggestions of an anatomical feto maternal separation (7 38) antigen immaturity of the fetus (34 38) or blocking of trophoblast antigens (6) were all partly abandoned when it was shown that the immunological suppression involved was not restricted to the placenta This systemic in vivo depression of lymphocyte functions has been shown by prolonged survival of skin grafts in pregnant rabbits (27) diminished response to intradermally injected PPD (21) and weakened defence to viral infections such as hepatitis (15) influenza (26) and polio-myelitis (2) in pregnant women These suppressive factors were early proposed to be polypeptide hormones produced by the trophoblastic cells and evidence that human chorionic gonadotrophin (HCG) and human chorionic somatotrophin (HCS) are immunosuppressive was suggested when it was found that hormones extracted from urine in pregnancy inhibited T cell proliferation induced by mitogens (1 12 25 28 31) antigens (24 25) or allogeneic cells (5 31) However humoral immunity to histocompatability antigens as well as other fetal antigens is readily induced during pregnancy (3 10 19 20 23 37) which may endanger its successful outcome

Conflicting data have been presented on the influence of placental hormones on B cell activation and both stimulatory (16 28 36) and inhibitory (4 36 53) effects have been recorded We have therefore restudied the influence of HCG and HCS on the in vitro lymphocyte activation induced by mitogens in human lymphoid cells Since thyroid stimulating hormone (TSH) shares the alpha-chain subunit with HCG (50) we investigated whether this hormone would exert immunosuppressive acitivity Human growth hormone (HGH) exhibiting amino-acid homology as well as partial biological cross reactivity (32 45) with HCS was also similarly tested

MATERIAL AND METHODS

Cells Lymphocytes from peripheral blood of healthy donors were separated on a Ficoll isopaque density gradient (Nyegaard Oslo Norway) Lymphocytes from tonsils removed from patients with chronic tonsillitis andenoids obtained from children or spleens from cadaveric kidney donors were prepared by pressing the tissue through a steel mesh into a balanced salt solution and thereafter washing the cells extensively Mouse spleen lymphocytes from C57Bl or CBA mice (of both sexes) from our own colony were also handled in the above mentioned way

Culture conditions The cells were cultured in a Mishell Dutton medium supplemented with or without heat inactivated human A or AB-serum For measurement of DNA synthesis cells were cultured in Micro Test II tissue culture plates (Falcon Plastics Oxnard Calif USA) with 2×10^5 human cells or 5×10^5 mouse spleen cells/0 2 ml culture For determination of plaque forming cells (PFC) the culture

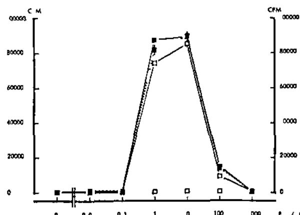


Fig 1 Suppressive effect of HCG on mitogen induced responses in human peripheral blood lymphocytes cultured for 3 days in A serum supplemented cultures (150 000 cells/culture) 0 (■—■) 20 IE/ml (■ ■) 200 IE/ml (□—□) or 2 000 IE/ml (□ □) of HCG was added at onset of cultures Results represent the mean of triplicate cultures ±SE

system of Fauci (18) was used Briefly cultures were set up in flat bottom plastic plates (3 cm diameter wells) (Nunc Roskilde Denmark) containing 5×10^6/ml human adenoid cells in 2 ml Mishell Dutton medium supplemented with 10 per cent heat inactivated SRBC absorbed human serum

Measurement of DNA synthesis 24 hours prior to harvest 0 02 ml of ^3H thymidine ($3\ 7\times10^1$ kBq) was added The cells were harvested with a Skatron harvesting machine (Oslo Norway) using distilled water collected on glass fibre dried overnight and thereafter transferred to plastic 0 3 ml of toluene based scintillation fluid was added he radio activity was measured in a scintillation spec)meter (TriCarb Packard Downer s Grove Ill A)

Measurement of PFC With some minor changes the procedure described by Fauci has been used (18) Processing of cell suspensions was begun within 60 min of removal of the tissue We found no disadvantage to using previously frozen human serum which had been repeatedly absorbed with sheep red blood cells (SRBC) Cultures were incubated for 72 or 96 hours which we found optimal for adenoid cells Unabsorbed guinea pig complement was used since no difference could be seen as compared to complement previously absorbed with SRBC

Mitogens Phytohemagglutinin (PHA) was purchased from Wellcome Research Laboratories (Beckenham Great Britain) and rabbit anti human beta$_2$ microglobulin from Dakopatt Reagents Copenhagen Denmark Lipopolysaccharide (LPS) from E Coli 055 B5 was kindly prepared by Professor T Holme Dept of Bacteriology Karolinska Institutet Stockholm Sweden Poke weed mitogen (PWM) was purchased from Techtum Instruments Umeå Sweden and Con A was obtained from Pharmacia Fine Chemicals Uppsala Sweden

Hormones Purified HCS was a gift from Pharmacia AB (Sweden) HCG was a gift from Organon AB (Askim Sweden) and from Leo AB (Helsingborg Sweden) HGH and TSH were gifts from Dr P Eneroth Karolinska Hospital Stockholm Sweden

Cytotoxicity assay The microcytotoxicity assay was carried out as follows Cell suspensions (10^7/ml in Mishell Dutton medium plus 10 per cent FCS) were set up in a 0 1 ml volume in plastic hemolysis tubes together with 0 1 ml ^{51}Cr labeled YAC tumor cells (10^5 cells/ml) The assay was harvested after 4 hours by spinning the remaining cells into a pellet and harvesting The supernatant and pellets were counted on a Nuclear Chicago gamma counter The per cent isotope release was calculated using the formula

$$\text{per cent isotope release} = \frac{\text{cpm supernatant bg}\times100}{\text{cpm supernatant}+\text{pellet 2 bg}}$$

RESULTS

Pregnancy associated hormones inhibit the lymphocyte response to T cell mitogens Human peripheral blood lymphocytes or human spleen lymphocytes were cultured with PHA in the presence of increasing amounts of polypeptide hormone As can be seen from Fig 1 the proliferative response to the mitogen was markedly inhibited by HCG in physiological concentrations This blocking effect was neither due to absorption of PHA by the hormone or competition for lectin binding sites on the lymphocytes since higher mitogen concentrations could not overcome the suppression (Fig 1) nor was due to decreased cell survival (data not shown)

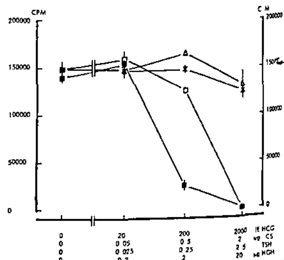


Fig 2 Effect of TSH (△) HGH (×) HCS (■) or HCG (□) on PHA induced responses (10 ug/ml) in human peripheral blood lymphocytes cultured for 3 days in A serum supplemented cultures (150 000 cells/culture) Results represent the mean of triplicate cultures ±SE

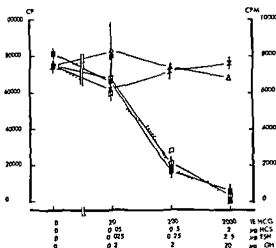


Fig 3 Effect TSH (△) HGH (×) HCS (■) or HCG (□) on human tonsil lymphocytes cultures for 3 days in A serum supplemented cultures and stimulated with anti human beta (—) microglobulin diluted 1 4 (left axis) or LPS 100 ug (right axis) ( ) *Results represent the mean of triplicate* cultures ±SE

A marked inhibition of the optimal PHA response was also induced by HCS whereas TSH and HGH were ineffective even in supranormal concentrations (Fig 2)

Effect of HCG and HCS on lymphocyte response to B cell mitogens Since antibodies directed against fetal antigens could also play a role in a possible rejection process glucoprotein hormones were investigated for their inhibitory effect on B cell proliferation and differentiation induced by B cell mitogens

The first group of experiments involved human tonsil cells and human spleen cells cultured with LPS and anti human beta₂ microglobulin together with increasing doses of hormone added at the onset of culture As seen in Fig 3 both mitogens induced a marked proliferative response in all cells tested and again this response was inhibited by both HCG and HCS *whereas TSH and HGH were devoid of immunosuppressive* effects

In the second series of experiments the influence of HCG on antibody formation was studied The ability to form antibodies was suppressed when HCG in increasing doses was added to the cultures from the start of cultivation (Table I) Furthermore a virtual total loss of plaque formation was noted when HCG was added directly in the PFC assay (Table I) possibly reflecting its anti-complementary effect

Immunosuppressive capacity of HCG on mouse lymphocytes Human placental hormones which were shown previously to cross react with other species were also tested for their inhibitory effect upon activation of mouse spleen lymphocytes by B and T cell mitogens and a substantial depression was noted (Table 2) This system offered an advantage for studying whether the inductive or expressive phase of immune functions was inhibited since the system for direct antibody complement independent cytotoxicity is well established in the mouse Thus circumventing the problem of the anti-complementary effect of HCG As seen in Table 3 no effect was noted on the cytotoxicity expressed by Con A activated cells on YAC *tumor* cells

DISCUSSION

In this paper we have confirmed earlier findings of the immunosuppressive action of HCG and HCS on T cell proliferation (1 12 25 28 31) HCG has previously been found either to suppress (4 36 53) or enhance (16 28 36) B cell responses In our hands profound suppression of mitogen induced B cell proliferation and differentiation was noted The addition of HCG in the PFC assay inhibited plaque formation possibly reflecting its anti-complementary effect

Another glucoprotein hormone TSH sharing the alpha chain subunit with HCG was devoid of effect which tends to imply that the immunosuppressive properties of HCG is due to the structure of the beta chain which is also responsible for the majority of other biological effects induced by the hormone HGH in spite of its biological cross reactivity with HCS was also totally ineffective

The immuno suppressive effect of HCG was first described in 1973 (1) and has since been confirmed in many reports The mechanism underlying the sup-

Table I *Suppression of plaque formation induced by 20 ug PWM in human adenoid cells by HCG*

Amount of HCG (IE) added	IgM anti SRBC PFC/10⁶ cells: Added at onset of culture	Added directly in the PFC assay
0	201	300
100	216	n t
500	236	767
1 000	140	290
2 000	100	161
5 000	n t	48

Background cul es co tained 5 IgM ant SRBC PFC/10⁶ cell

Table II *Effect of HCG on the mitogen induced pro liferation of CBA mouse spleen cells cultured in se rum supplemented medium for two days Results are mean net cpm of triplicate cultures*

Amount of HCG (IE) added	LPS (100 ug/ml)	PHA (1 ug/ml)
0	26 298	127 343
200	25 613	87 120
1 000	5 240	29 243
2 000	2 050	8 105

pressive effect is however still poorly understood Cell death does not appear to be involved since cell survival in cultures containing HCG was not affected Nor does the inhibition at least in our hands seem to result from a mere competition between HCG and mitogen for binding sites on the lymphocytes since higher doses of mitogen did not overcome the sup pression which is in contrast to previous findings (9)

The hypothesis that HCG would act by increasing the intracellular content of AMP has recently receiv ed substantial experimental support (14 51) The assumption is also in agreement with the lack of sup pression of B cells (52) concomitant with an inhibi tion of T cells reported by some investigators (16 28 41) However since no differential suppressive effect on B and T cells was found in our experiments nor in dies conducted by others (4 39) this mechanism unlikely

It has been claimed that the immuno suppression exhibited by HCG is simply due to contaminating proteins suggested to be either immunoglobulin (35) non immunoglobulin (39) or of underdetermined (9 36 53) character Although the disparity between the different studies allows no definite conclu ion as to the chemical nature of the immuno suppressive com ponent the data on the inhibitory effect on cell activa tion by IgG either eluted from the placenta (19 47) or extracted from serum (48) tend to support the first notion Theoretically inhibition of maternal lym phocytes during pregnancy by IgG could be achieved either by blocking of the HLA D determinants induc ing the rejection process (46) or by interfering with the triggering receptor on the cells Since anti mitogen receptor antibodies seem to induce an im mune response rather than inhibiting it (13) the latter consideration does not seem valid Furthermore maternal antibodies have been found to coat fetal lymphocytes (11 33 49) thus supporting the first no tion Again conflicting data have been put forward on the actual presence of anti HLA antibodies in placental extracts (29 30) thus obscuring the inter pretation However since pure immunoglobulin free HCG still exhibits suppressive properties (4) at least some preparations show association between the hormone and immuno suppression

The non immuno suppressive effect of pure HCG in small doses as compared with its inhibitory effect in large doses is a matter of controversy This however is not contradictory to the assumption tha HCG is a pregnancy retaining factor since it ha been shown that local concentrations of HCG sur rounding the trophoblast exceed 10 000 units pe millilitre of interstitial fluid on the tenth day o pregnancy (8) and we have earlier shown tha retroplacental lymphocytes were significantly sup pressed in their mitogen responsiveness as compare to cubital vein lymphocytes (22)

The apparent cross reactivity between huma chorionic gonadotrophin and gonadotrophins fron other species (4 16 17 25 36 53) offered simplified animal system for determining the effect of HCG DNA synthesis induced by mitogens wa clearly able to be inhibited by HCG Since the ex pressive phase of cytotoxicity was not affected w conclude that at least in this respect an ongoing im mune response cannot be inhibited by HCG Thes data are also in full accordance with findings on th PHA induced mitogenicity in human lymphocyte (24) where HCG had to be added from the initiatio of culture in order to be effective

Taken together our data seem compatible with th suggested role of HCG in the maternal toleranc towards the histoincompatible fetus Whether th glucoprotein constitutes the major immuno-suppres

Table III *Effect of HCG on the Con A induced cyto toxicity of CBA mouse spleen cells on* ^{51}Cr *labele YAC tumor cells Results which were recorded afte 4 hours of incubation are the mean net per cent lysi on triplicate assavs*

Amount of HCG (IE) added in the test	Amount of Con A used for pre activation		
	0	5 ug/ml	10 ug/ml
0	−3 6	5 5	2 75
100	−2 8	5 0	4 55
500	−1 55	4 85	3 7
1 000	−1 05	5 25	1 75
2 000	−2 1	4 0	7 35

sive factor or whether other steroid hormones such as progesterone (40 43 44) estrogen (43 44) or corticosteroids (42 44) which also display immunoregulatory properties contribute to the successful outcome of pregnancy remains to be evaluated

ACKNOWLEDGEMENTS

This work was supported by the Swedish Cancer Society the Alex and Eva Wallström Foundation for Scientific Research and the Åke Wiberg Foundation The excellent technical assistance of Ms Caroline Mohlström is gratefully acknowledged We are furthermore indebted to Dr Peter Eneroth Karolinska Hospital Stockholm Sweden for supplying us with some of the hormones used in this study

REFERENCES

1 Adcock E W Teasdale F August C S Cox S Meschia G Battaglia F C & Naughton M C Human chorionic gonadotropin Its possible role in maternal lymphocyte suppression Science 181 845 1973
2 Anderson G W Anderson G Skaar A & Sandler F Polymyelitis in pregnancy Am J Hyg 55 127 1957
3 Baines M G Ansell J M Laren A & Micklem H S Maternal immunization to paternal antigens in multiparous mice J Reproduc Fertil 42 293 1975
4 Beck D Ginsburg H & Naot Y The modulating effect of human chorionic gonadotropin on lymphocyte blastogenesis Am J Obstet Gynecol 129 14 1977
5 Beling C G & Weksler M E Suppression of mixed lymphocyte reactivity by human chorionic gonadotrophin Clin Exp Immunol 18 537 1974
6 Billingham R E Transplantation immunity and the maternal fetal relation N Engl J Med 111 469 1971
7 Billingham R E Transplantation immunity and the maternal fetal relation N Engl J Med 270 667 1964
8 Braunstein G C Grodin J H Vaitukaitis J & Ross G T Secretory rates of human chorionic gonadotropin by normal trophoblast Am J Obstet Gynecol 115 447 1973
9 Caldwell J S Stites D P & Fudenberg H H Human chorionic gonadotropin Effects of crude and purified preparations on lymphocyte responses to phythemagglutinin and allogeneic stimulation J Immunol 115 1229 1975
10 Carbonara A Trinchieri G & Massobrio M Antibodies in parous women detected by antibody dependant cell mediated cytotoxicity Tissue Antigens 4 558 1974
11 Ceppellini R Old and new facts and speculations about transplantation antigens of man In Progress in Immunology (ed D B Amos) p 973 Acad Press New York 1971
12 Contractor S F & Davies H Effect of human chorionic somatomammotrophin and human chorionic gonadotropin on phytohaemagglutinin induced lymphocyte transformation Nature New Biol 243 284 1973
13 Coutinho A Forni L & Watanabe T Genetic and functional characterization of an antiserum to the lipid A specific triggering receptor on murine B lymphocytes Eur J Immunol 8 63 1978
14 Daughaday W H In Textbook of Endocrinology ed 5 (ed R H Williams) p 42 W B Saunders Co Philadelphia 1971
15 D Cruz J A Balanini S G & Iyer L S Infectious hepatitis and pregnancy Obstet Gynecol 31 449 1968
16 Fabris N & Piantanelli L Effect of chorionic gonadotropins on humoral and cell mediated immunity 5th Int Conf of lymphatic tissue and germinal centers Tiberias Israel June 24-30 1975
17 Fabris N Piantanelli L & Muzzioli M Differential effect of pregnancy or gestagens on humoral and cell-mediated immunity Clin Exp Immunol 29 306 1977
18 Fauci A S & Pratt K R Activation of human B lymphocytes I Direct plaque forming cell assay for the measurement of polyclonal activation and antigenic stimulation of human B-lymphocytes J Exp Med 144 674 1976
19 Faulk W P Jeannet W D & Carbonara A Characterization of immunoglobulins on trophoblastic basement membranes J Clin Invest 54 1011 1974
20 Faulk W P van Loghem E & Stickler G B Maternal antibody to foetal light-chain (Inv) antigens Am J Med 56 393 1974
21 Finn R St Hill C A Govan A J Ralfs J G Gurney F J & Denye V Immunological responses in pregnancy and survival of fetal homograft Br Med J 3 150 1972
22 Fuchs T Hammarström L Smith E & Brundin J In vivo suppression of uterine lymphocytes during early human pregnancy Acta Obstet Gynecol Scand 56 151 1977
23 Fudenberg H H & Fudenberg B R Antibody to hereditary human gammablobulin (Gm) factor resulting from maternal fetal incompatibility Science (Washington 145 1 0 1964
24 Han T Inhibitory effect of human chorionic gonadotrophin on lymphocyte blastogenic response to mitogen antigen and allogeneic cells Clin Exp Immunol 18 529 1974
25 Han T Human chorionic gonadotropin Its inhibitory effect on cell mediated immunity in vivo and in vitro Immunology 29 509 1975
26 Hardy J M B Azarowicz E N Mannini A Medearis D N Jr & Cooke R E The effect of asian influenza on the outcome of pregnancy Baltimore 1957 1958 Am J Pub Health 51 1182 1961
27 Heslop R W Krohn P L & Sparrow E M The effect of pregnancy on the survival of skin homografts in rabbits J Endocrinol 10 325 1954
28 Hsu C C S & Samuel J Peripheral blood lymphocytes responses to phythemagglutinin and pokeweed mitogen during pregnancy J Proc Soc Exp Biol Med 146 771 1974
29 Jeannet M Faulk W P Crighton W D & Fourner K Blocking of mixed lymphocyte cultures by Ig G

eluted from human placenta Abstr 8th Leukocyte Culture Conf Uppsala Sweden 1974

30 Jeannet M Werner C Ramirez E Vassalli P & Faulk W P Anti HLA Anti human Ia like and MLC blocking activity of human placental Ig G Transplantation Proc *9* 1417 1977

31 Kaye M D & Jones W R Effect of human chorionic gonadotropin on in vitro lymphocyte transformation Am J Obstet Gynecol *109* 1029 1971

32 Lesniak M A Roth J Gorden R & Gavin III J R Human growth hormone radio receptor assay using cultured human lymphocytes Nature New Biol *241* 20 1973

33 Leventhal B G Buell D N Terasaki P Yankee R & Rogentine G N The mixed leukocyte response Effect of maternal plasma *In* Proceedings Vth Leukocyte Culture Conf (ed J Harris) p 473 Acad Press New York 1970

34 Little C C The genetics of tissue transplantation in mammals J Cancer Res *8* 75 1924

35 Loke Y W & Pepys M B Effects of human chorionic gonadotropin preparations on complement in vitro Am J Obstet Gynecol *121* 37 1975

36 Maes J R F & Clavarie N The effect of preparations of human chorionic gonadotropin on lymphocyte stimulation and immune responses Immunol *33* 351 1977

37 McConnel R B The prevention of Rh haemolytic disease Ann Rev Med *17* 291 1966

38 Medawar P B Some immunological and endocrinological problems raised by the evolution of viviparity in vertabrates Symposia of the Soc for Exp Biol *77* 320 1953

39 Morse J H Stearns G Arden J Agosto G M & Canfield R E The effects of crude and purified human gonadotropin on in vitro stimulated human lym te cultures Cell Immunol *25* 1778 1976

roe J S Progesterons as immunosuppressive ts J Reticuloendothel Soc *9* 361 1971

Murgita R A The immunosuppressive role of alpha fetoprotein during pregnancy Scand J Immunol *5* 1003 1976

42 Pasqualini J R Neyen B L Uhrich F Wiquist N & Diczfalusy E Cortisol and cortisone metabolism in the human foetoplacental unit at mid gestation J Steroid Biochem *1* 209 1970

43 Schmidt W Lenhard V Schackert K & Runnebaum B Inhibitory effect of gestagens and estrogens on lymphocyte response induced by stimulation with mitogen and allogeneic lymphocytes Abstr 10th Leukocyte Culture Conf Amsterdam The Netherlands Sept 10-13 1975

44 Schmidt W Lenhard K Schackert K & Runnebaum B Der inhibitorische Effekt von Östrogenen und Gestagenen auf die Lymphozyten Transformation nach mitogener und allogener Stimulation 7th Ann meeting of the germ tissue typing Labs p 297 1975

45 Sherwood L M Handwerger S McLaurin W D & Lanner M Amino acid sequence of human placental lactogen Nature New Biol *233* 59 1971

46 Smith R T The immunobiology of abortion N Engl J Med *295* 1249 1976

47 Svehag S E & Schilling W Synergism between alloantibodies of F (ab[1]) 2 and prednisone on the survival of murine split heart allografts Transplantation *15* 345 1973

48 Taylor V P & Hancock K W Antigenicity of trophoblast and possible antigen masking effects during pregnancy Immunol *28* 973 1975

49 Tiilikainen A Schröder J & de la Chapelle A Fetal leukocytes in the maternal circulation after delivery Transplantation *17* 355 1974

50 Vaitukaitis J L & Ross G T Subunits of human glycoprotein hormones Their immunological and biological behavior Israel J Med Science *10* 1280 1974

51 Villee C A & Gabbe S G Effects of gonadotropins on placental steroid genesis *In* Gonadotropins (eds B B Saxena C G Beling and H M Gandy) p 309 Wiley Interscience Publ New York 1972

52 Vischer T L & Lospalluttio J J The differential effect of cholera toxin on the lymphocyte stimulation induced by various mitogens Immunol *29* 275 1975

53 Younger J B St Pierre R L & Zmiljewski C M Effect of human chorionic gonadotropin on antibody production Am J Obstet Gynecol *105* 9 1969

Submitted for publication July 27 1978

Tommy Fuchs M D
Department of Obstetrics and Gynecology
Danderyd Hospital
S 182 88 Danderyd
Sweden

Acta Obstet Gynecol Scand 58 423–427 1979

PLASMA PROGESTERONE SERUM ESTRIOL AND PLASMA HPL DETERMINATIONS DURING THE LAST TRIMESTER TO DETECT CHANGES BEFORE SPONTANEOUS LABOR

Comparison of progesterone assay using RIA and CPB

B Ottesen and P E Lebech

From the Department of Gynecology and Obstetrics Frederiksberg Hospital Copenhagen F Denmark

Abstract Conflicting results have been published regarding changes in plasma progesterone during the last trimester of pregnancy Some have demonstrated a fall in plasma progesterone before labor and this has been taken as a possible explanation of the onset of labor It has been suggested that the various results could be due to differences in methods for progesterone determination

In this study the progesterone levels were determined by both RIA and CPB In 11 women the plasma progesterone human placenta lactogen and serum estriol were measured weekly during the last trimester of normal pregnancies and immediately after delivery All samples were analysed radioimmunologically In order to compare the radioimmunoassay and competitive protein binding techniques (RIA and CPB) the progesterone levels were determined by both methods This was also done for 80 successive plasma progesterone routine samples drawn from women who were not pregnant or who were in the early stages of pregnancy

Both methods showed a significant rise in the plasma progesterone level during the last 6 weeks before spontaneous labor However the values obtained were lower when assayed by CPB than by RIA presumably because of a higher specificity and a cross reaction in RIA

Serum estriol exhibited increasing values throughout pregnancy but without a significant rise during the last few weeks

Plasma HPL settled at a constant level during the last few weeks before labor

Plasma progesterone determinations during the last trimester of pregnancy have given many conflicting results especially during the last 5 weeks before the onset of spontaneous labor

Some authors have found a significant fall in plasma progesterone during the last 5 weeks before term First this was demonstrated by the competitive protein binding technique (3) and later by radioimmunoassay (15) This has been taken to confirm the early hypothesis on the relaxing effect of progesterone upon the uterine muscle

Others (4 6 7 9) have demonstrated first by means of the competitive protein binding technique (CPB) and later by investigating the free and bound fraction of progesterone by radioimmunoassay (RIA) an increase throughout pregnancy (1 12)

Unconjugated estradiol 17β and unconjugated polar estrogens (estriol plus other C 15 or C 16 substituted estrogens) have previously been found by most workers (6 7 10 11 13 14) to rise towards term

Chorionic somato mammotropin (HCS) has previously proved to adjust to a constant level during the last weeks before labor (2 8) Turnbull *et al* have advanced several suggestions to explain the many different results found for plasma progesterone RIA affords greater specificity since it does not include the metabolites 20 α-dihydroprogesterone and 17 α hydroxyprogesterone as does the CPB technique The material may not consist of normal patients and the samples may not have been taken serially so that the results are influenced by inter patient variations Often the number of patients has been too small no decrease has been demonstrated in one third of the patients

The present study therefore was designed to follow the variation in plasma progesterone and HPL as well as the serum estriol during the last 5 weeks before the onset of spontaneous labor in normal pregnant women paying particular attention to the named factors in determining plasma progesterone by using both methods (RIA and CPB) concurrently in an attempt to explain the discrepancy between earlier results

MATERIAL AND METHODS

The material comprises 11 pregnant women who knew the date of the last menstrual period and had had a regular menstrual cycle Five were treated during the pregnancy with chlorthalidone (Hygroton®) because of edema and one had to be delivered by acute cesarean section because of cord complications

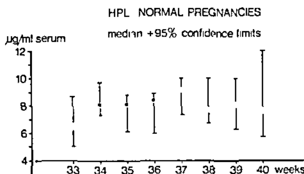


Fig 1 HPL levels in µg/ml with median ±95 per cent confidence limits plotted against week of pregnancy

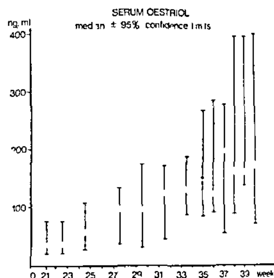


Fig 2 Serum estriol in ng/ml with the median ±95 per cent confidence limits plotted against week of pregnancy

All 11 went spontaneously into labor at expected term ±6 days all passed clear amniotic fluid and delivered infants weighing 3 000 – 4 250 g length 48 – 57 cm with an apgar score of 9 – 10 one minute after birth None of the placentae showed infarcts signs of bleeding or other forms of degeneration All patients had peripheral venous blood drawn from the cubital vein weekly during the last 6 weeks before expected term a few weekly from the 24th week and one sample immediately after delivery of the placenta The samples were immediately centrifuged and the plasma or serum was stored at −20 C and later analysed simultaneously for each patient RIA was used for the estriol HPL and progesterone assay and also the CPB technique for progesterone

Moreover 80 consecutive routine samples from in patients (non pregnant or in the 6th – 12th week of pregnan were assayed by CPB as well as RIA of progesterone

Diethyl ether Analar R BDH Chemicals Ltd England Ethanol re distilled from the Hospital Sterilized aqua purissima from the Hospital

Buffer stock solution Na PO_4 H_2O 13 8 g NaN_3 2 0 g adjusted by NaOH and distilled water to pH 7 4±0 1 made up to 1 litre

Assay buffer Bovine serum albumin 20 g buffer stock solution 500 ml distilled water made up to 1 litre

Norrit suspension 0 9 g NaCl 100 ml stock buffer solution 0 05 g dextran T 70 0 6 Norrit A neutral charcoal

Non radioactive progesterone Δ [4]pregnene 3 20-dione (Sigma) dissolved in re distilled ethanol Checked by silica gel chromatography in a dichlormethane 80 acetone 20 system against 17-α hydroxyprogesterone and 20-α hydroxyprogesterone

Progesterone 1 2 H^3 0 25 mCi 0 0017 mg in 0 25 ml New England Nuclear Dilutes 1 10^4

Antiserum Gift from Lederle Laboratories R J Saldarini Ph D batch 755 Rivanol (2 ethoxy 6 9 diaminoacridine lactate hydrate) precipitated Used in a 1 1500 dilution mean binding 55 per cent which gave most linearity on the standard curve

Scintillator fluid Insta gel Packard

Procedure

Extraction 0 5 ml plasma is shaken for 10 min with 4 ml diethyl ether Having been left at 20 C for 30 min the supernatant is transferred to clean tubes and evaporated under N air current at 37 C

Extract of samples from non pregnant and from pregnant women before the 12th week Re dissolve in 1 ml re-distilled ethanol

Extract of samples from pregnant women Re dissolve in 10 ml re distilled ethanol

The samples are mixed and 200 100 50 and 25 µl respectively pipetted off into test tubes and evaporated under N_2 at 37 C

Radioimmunoasssay To the evaporated samples 0 1 ml assay buffer 0 1 ml assay tracer (about 10 000 c p m) and 0 1 ml antiserum are added and mixed Incubation for 1 hour at +4 C 0 5 ml Norrit suspension is added and the

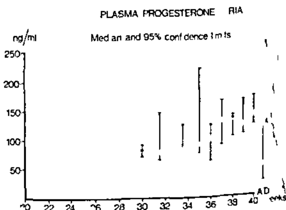


Fig 3 Plasma progesterone in ng/ml assayed by RIA as the median ±95 per cent confidence limits plotted against week of pregnancy a d = after delivery

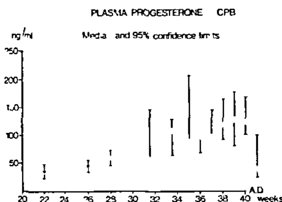


Fig 4 Plasma progesterone in ng/ml assayed by CPB as the median ±95 per cent confidence limits plotted against week of pregnancy a d = after delivery

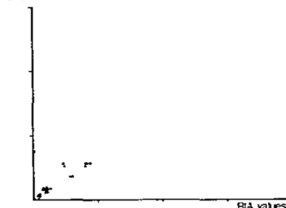


Fig 5 Routine sample determinations of plasma progesterone Ordinate CPB levels in ng/ml and abscissa RIA levels in ng/ml

tubes are left for another 10 min after mixing Centrifugation for 5 min at 2 000 rpm 0 6 ml of the supernatant is counted after adding 10 ml scintillator fluid

RIA of chorionic somatomammotropin (HCS HPL) These determinations were carried out in the Hormone Laboratory of Dept F Fredriksberg Hospital by a principle described previously (8)

RIA of total estriol (E_3) following enzymic hydrolysis Estriol RIA kit from the Radiochemical Centre Amersham Buckinghamshire England

Determination of plasma progesterone using the competitive protein binding technique

The method described by Johansson (5) was used with the modification that samples from the last trimester were diluted 0 times with aqua purissima and thereof 0 5 ml was removed for extraction

RESULTS

In Fig 1 the HPL values in µg/ml with the median ±95 per cent confidence limits are plotted against week of pregnancy The values settle at an almost constant level during the weeks just before term The values for the individual weeks were tested mutually by the Mann Whitney rank sum test and 2α was in all cases $>0\ 10$

Fig 2 presents the serum estriol in ng/ml with the median ±95 per cent confidence limits plotted against week of pregnancy The values rose towards term but without any significant increase during the last 5–6 weeks before the onset of spontaneous labor $2\alpha > 0\ 10$ in the Mann Whitney rank sum test

Fig 3 illustrates the plasma progesterone in ng/ml measured by RIA as the median ±95 per cent confidence limits plotted against week of pregnancy The values increase towards term There is a significant difference between the values in the 40th week and those in the 36th week 2α being $<0\ 05$ in the Mann Whitney rank sum test

Fig 4 sets out plasma progesterone in ng/ml assayed by CPB with the median ±confidence limits plotted against week of pregnancy The values increase towards spontaneous labor There is a significant difference between the values in the 40th week and those in the 36th week $2\alpha<0\ 10$ in the Mann Whitney rank sum test

Fig 5 gives the routine sample determinations of plasma progesterone Ordinate CPB values in ng/ml and abscissa RIA values in ng/ml

The correlation coefficient is 0 89 the slope of the regression line $\alpha = 0\ 52$ and the intercept $= 2\ 2$ The values measured by RIA are significantly higher than those measured by CPB $2\alpha<0\ 05$ in Wilcoxon s paired rank sum test

Comparison of RIA and CPB in the progesterone assays sensitivity RIA differs 15 pg from 0 on the

Table I *Precision of CPB and RIA*

Read ng interval on the standard curve	Coefficient of variation as percentage (n = 40)
CPB	
0 1 – 1 0 ng	16
1 0 – 5 0 ng	8
RIA	
15 – 1 000 pg	8

Th inaccuracy of the analysi was calculated on the basi of d plicate determ ation

Table II *Specificity Per cent recovery of steroid (2–5 ng) with 0 5 ml plasma added and extracted with 10 volumes of petroleum ether (CPB)*

Steroid	Recovery as percentage
Progesterone 4 ^{14}C	95
17α hydroxyprogesterone 4 ^{14}C	25
11β hydroxyprogesterone	11

standard curve CPB differs 100 pg from 0 on the standard curve In table I is given the precision of CPB and RIA The specificity of the extraction with petroleum ether (CPB) is given in Table II The recovery of corticosterone and cortisol has been found to be negligeable The cross reaction in the two assays are given in Table III

DISCUSSION

The results for serum estriol and HPL proved to be in accordance with previous findings (7 10 11 13 14)

Progesterone assays revealed a significant increase during the last 6 weeks before labor both when using CPB and RIA

This too is in conformity with previous findings (1 7 9)

T t was not possible to confirm the fall in plasma during the weeks before spontaneous la was demonstrated by Turnbull *et al* (3 15) others Although attention was paid in the ex set up to the sources of error pointed out by Turnbull *et al* (15) viz choice of method patient material and analytical method the present study did not confirm Turnbull *et al* s results or hypotheses as to the reason why others have not been able to demonstrate a fall in the plasma progesterone con

Table III *Cross reaction† without extraction*

Steroid	RIA %	CPB %
Progesterone	100	100
17α OH progesterone	1 4	190
20α dihydroprogesterone	0 5	142
Testosterone	0 05	37
5α pregnane 3 2 dione	*31*	*0*
11β hydroxyprogesterone	0	150
5β pregnane 3-01 20-one	0	0

$$\dagger\ CR_{50\%} = \frac{\text{pg steroid progesterone with 50\% bind g} \times 100}{\text{pg steroid X with 50\% binding}}$$

Table IV *Recovery experiments performed in plasma*

RIA	74 per cent	(n = 10)
CPB	62 per cent	(n = 16)

centration and thereby afford a possible explanation for the onset of labor

Comparison of CPB and RIA determinations showed significantly higher values with RIA This is explicable in part by higher recovery and in part by a certain cross reaction with 5α pregnane 3 20-dione which occurs in a concentration of 20–40 ng/ml during the weeks immediately before term (12)

In conclusion the present study did not afford results to support the theory of a withdrawal of the protective influence of progesterone upon the myometrium as a factor in the spontaneous onset of labor

REFERENCES

1 Batra S Bengtsson L P Grundsell H & Sjöberg N O Levels of free and protein bound progesterone in plasma during late pregnancy J Clin Endocrinol Metab *42* 1041 1976

2 Christensen A Fröyshov D & Fylling P Hormone and Enzyme assays in Pregnancy Acta Endocrinol *76* 201 1974

3 Csapo A I Knobil E Molen H J van der & Wiest W G Peripheral plasma progesterone levels during human pregnancy and labor Am J Obstet Gynecol *110* 630 1971

4 Dawood Y & Eng Soon Teoh Disappearance of serum progesterone after normal delivery and removal of hydatidiform mole Obstet Gynecol *45* 9 1975

5 Johansson E D B A simplified procedure for the assay of progesterone Karolinska symposia on research methods in reproductive endocrinology 2nd symposium 188 1970

6 Klopper A & Shaaban M Variability of fetoplacental steroids in maternal plasma in late pregnancy Obstet gynecol *44* 187 1974

7 Klopper A Jandial V & Wilson G Plasma steroid assay in the assessment of fetoplacental function J Steroid Biochem *6* 651 1975

8 Lebech P E & Borggard B Serum levels of human chorionic somatomammotropin (HCS) in normal and abnormal pregnancies Acta Endocrinol *75* Supplement 182 35 1974

9 Lindberg B S Nilsson B A & Johansson E D B Plasma progesterone levels in normal and abnormal pregnancies *Acta Obstet Gynecol Scand 53* 329 1974

10 Macourt D Corker C S & Naftolin F Plasma oestriol in pregnancy Br J Obstet Gynecol *78* 335 1973

11 Masson G M Plasma oestriol concentration during normal pregnancy Br J Obstet Gynecol *80* 201 1973

12 Milewich L Gomez Sanchez C Madden J D & Macdonald P C Isolation and characterization of 5α Pregnane 3 20-dione and progesterone in peripheral blood of pregnant women Measurement throughout pregnancy Gynecol Invest *6* 291 1975
13 Shearman R P Jools N D & Smith I D Maternal and fetal venous plasma steroids in relation to parturition Br J Obstet Gynaecol *79* 212 1972
14 Stafford J E H A versatile radioimmunoassay for the determination of serum oestriol in pregnancy Ann Clin Biochem *10* 159 1973
15 Turnbull A C Flint A P F Jeremy J Y Patten P T Keirse M J N C & Anderson A B M Significant fall in progesterone and rise in oestriol levels in human peripheral plasma before onset of labor Lancet *1* 101 1974

Submitted for publication January 11 1978

B Ottesen M D
Kroghsgade 6 II TH
DK 2100 Copenhagen Ö
Denmark

SEGMENTAL EPIDURAL ANALGESIA FOR LABOR AND DELIVERY

D Gal R Choudhry K A Ung A Abadir and M L Tancer

From the Departments of Obstetrics and Gynecology and Anesthesia The Brookdale Hospital Medical Center Brooklyn New York USA

Abstract A study to evaluate segmental epidural analgesia in labor is described Bupivacaine (0 25 per cent) was used during the first stage of labor and for the second stage either 3 per cent Chloroprocaine delivered through the catheter (Group I) or 1 per cent Lidocaine as a perineal infiltrate (Group II) was used There were 124 full term patients of whom 36 were nulliparous and 88 were multiparous The effects of segmental epidural analgesia on maternal blood pressure pain relief preservation of lower limb motor power duration and progress of labor and fetal outcome were evaluated Pain relief during the first stage of labor was satisfactory in 114 (92 per cent) of the patients There were no significant changes in maternal blood pressure motor power in lower limbs efficiency of uterine contractions and internal rotation of the presenting part when analgesia was effective The use of 2-Chloroprocaine for second stage pain relief required low forceps delivery in 84 (91 per cent) patients as compared to 14 (44 per cent) patients that had 1 per cent Lidocaine local infiltration Fetal outcome was excellent in all cases in that the one minute Apgar score was never lower than 7

The objective of obstetric anesthesia is to provide maximal pain relief with minimal fetal and maternal risk and with minimal interference with the normal course of labor Relief of first stage labor pain requires segmental analgesia at T 11 and T 12 (4) Continuous epidural analgesia using a single catheter technique is an efficient and controllable method of providing such pain relief during both labor and delivery (3)

Bupivacaine was elected to be the anesthetic agent during the first stage of labor because of its advantageous pharmaceutical qualities It affects sensory fibers while sparing most motor fibers (3 9) Therefore there is less paralysis of perineal muscles and hence less interference with internal rotation of the presenting part (1) Similarly there is little or no paralysis of the abdominal and intercostal muscles thus enabling the parturient to bear down forcefully during the second stage (3) In contrast to Bupivacaine 2 Chloroprocaine has an ester bond and is rapidly metabolized by pseudochlinesterases it has a rapid onset of effect and short duration of action (7) Therefore it was used for (second stage) pain relief during delivery

The aims of this study are to evaluate

a The effect of 0 25 per cent Bupivacaine in 5 cc doses during first stage of labor as relates to pain relief maternal blood pressure and the progress of labor

b The effect of a single 10 cc dose of 3 per cent 2 Chloroprocaine for perineal pain relief during delivery

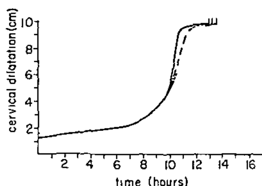
c The combined effect of the two drugs on the mode of delivery and fetal outcome

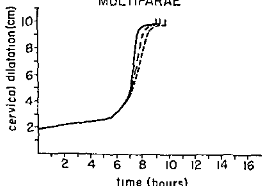
MATERIAL AND METHODS

There were 124 full term parturients each with an uneventful antepartum course and a vertex presentation Thirty six were nulliparous and 88 multiparous Parturients who gave a history of dizziness weakness or fainting attacks while in the supine position were rejected from the study Proper informed consents were obtained

Baseline internal fetal heart monitoring and intrauterine manometry were begun 15 minutes prior to the administration of epidural analgesia and continued thereafter Baseline maternal blood pressure was recorded in the left lateral and supine positions If a fall in blood pressure was greater than 10 per cent when turning from the lateral to the supine position 500 cc Lactated Ringers Solution and 500 cc 5 per cent Dextrose in water were given intravenously prior to analgesia Epidural analgesia was begun when cervical dilatation reached 4-6 cm in nulliparous and 3 5 in multiparous patients The catheter tip was advanced 4-5 cm past the bevel of a Touhy needle facing cephalad and 5 cc of 0 25 per cent Bupivacaine were injected Maternal blood pressure was recorded at least every 2 minutes for 15 minutes After relief of pain maternal blood pressure motor power in the lower limbs cervical dilatation station and internal rotating of the presenting part were checked at 30 minute intervals Chosen as an indication of preservation of motor power was the ability of the patient to elevate her lower limbs for 10 seconds An additional 5 cc dose of 0.25 per cent Bupivacaine was given when the parturient complained of return of labor pain

When crowning of the presenting part was observed 92 parturients were assisted to a sitting position and remained seated for one minute after injection of 10 cc of 3 per cent





Progress in dilatation in our two groups in com to a normal mean labor curve (Friedman) of pa ents without epidural analgesia

2 Chloroprocaine through the epidural catheter (Group I) A local perineal infiltrate of 10 15 cc of 1 per cent Lidocaine without Epinephrine was used in 32 patients for perineal pain relief (Group II)

RESULTS

1 Effects of epidural Bupivacaine during the first stage of labor

Blood pressure The mean blood pressure for all pa tients prior to analgesia was 124/76 (±10/8) mm Hg After administration of epidural Bupivacaine mean blood pressure recordings at 5 10 and 15 minutes were 120/68 (±12/9) 122/65 (±14/10) and 118/70 (±10/10) respectively Hypotension did not occur in any of the 124 patients

Pain relief pain relief was satisfactory in 114 pa tients Ten patients required supplementary doses of intravenous analgesia The subjective sense of well being was noted promptly after injection

The mean time interval between the initial and re peat dose of Bupivacaine was 75 (±15) minutes

Motor power preservation motor power as defined was preserved throughout the first stage of labor in 108 patients The remaining 16 patients were able to move their lower limbs but did not meet the test of leg elevation for 10 seconds

Internal rotation of the fetal vertex satisfactory in ternal rotation occurred in all but one patient A 15 year old black nullipara whose fetus remained in persistent occipito posterior position was delivered by cesarean section because of cephalopelvic dispro- portion

Uterine contractions As observed by intrauterine manometry these were unaffected in 110 patients Oxytocin stimulation was required in 14 patients of whom 8 were nulliparous and 6 multiparous because of diminution of frequency and intensity of uterine contractions

Duration of labor the mean time interval between induction of epidural analgesia and delivery was 3 hours 50 minutes (±32 minutes) for nulliparous and 2 hours 35 minutes (±24 minutes) for multiparous pa tients The mean progress of dilatation in both Groups I and II compares well with the normal curve described by Friedman (8) as shown in Fig 1

Fetal heart monitoring variable decelerations were observed in 9 patients and late decelerations in 2 shortly after the initiation of the epidural analgesia These patients responded well to repositioning into the left lateral recumbent position and the adminis tration of 6 liters/minute of oxygen via Venturi mask

2 Effects of 2 Chloroprocaine on the second stage of labor There were 92 Group I patients each of whom received 10 cc of 2 Chloroprocaine through the epidural catheter for terminal second stage analgesia *of these 8 delivered spontaneously* and 84 were delivered by low forceps All babies in this group had one minute Apgar scores of 7 or better as presented in Table I

3 Effects of local infiltration of 1 per cent Lido- caine on the second stage of labor

There were 32 patients in group II each of whom had local perineal infiltration of 10-15 cc of 1 per cent Lidocaine Of these 18 delivered spontaneously and 14 were delivered by low forceps All babies in this group had Apgar scores of 7 or better as shown in Table I

Table I *Comparison of effect of 10 cc 3 per cent 2 Chloroprocaine (Group I) and 1 per cent Lidocaine (Group II) on mode of delivery and fetal outcome*

	Spontaneous delivery No of patients	Apgar	Low forceps delivery No of patients	Apgar
Group I (92)	8 (9)	8 or above	84 (91)	7 or above
Group II (32)	18 (56)	8 or above	14 (44)	7 or above

the figures within parenthesis denote number of patients in per cent

DISCUSSION

Our findings are in agreement with those of Vasicka and Kretchmer (10 11 12) in that the quality and quantity of uterine contractions were not altered by epidural analgesia when hypotension did not occur

This study shows that segmental epidural analgesia given according to our protocol does not slow down the progress in dilatation or descent and does not prolong labor The mean progress in dilatation for nulliparous patients was 2 5 cm/hour (±0 5) and for multiparous patients was 4 cm/hour (±0 8) This compares well with the data described by Friedman as the course of normal labor (8)

Satisfactory pain relief was provided to 114 patients (92 per cent) which is in agreement with the success rate in other studies (1 4 6)

The fetal outcome in this study was good and all neonates had a one minute Apgar Score between 7 and 10 We believe that Bupivacaine has minimal effect on neonatal outcome as observed by Belfrage *et al* (2) The effect of 2 Chloroprocaine on fetal outcome is minimized by its rapid hydrolysis in maternal blood (3 5 7) that prevents it substantial transfer to the fetus

CONCLUSION

This technique of segmental epidural has been shown to provide good pain relief during the first stage of labor It does not interfere with the normal course of labor as relates to either dilatation or descent It is safe for the mother and fetus since neither hypotension nor fetal depression were encountered For these reasons we find segmental epidural used as described to be a good technique for general use when pain relief during labor is desired

REFERENCES

1 Akamatsu T J & Bonica J J Spinal and extradural analgesia anesthesia for parturition Clin Obstet Gynecol *17* 183 1974
2 Belfrage P Berlin A & Raabe N Lumbar epidural analgesia with bupivacaine in labor Drug concentration in maternal and neonatal blood at birth and during the first day of life Am J Obstet Gynecol *123* 839 1975
3 Bonica J J Principles and practice of obstetric analgesia and anesthesia p 611 F A Davis Co 1969
4 Bromage P R An evaluation of bupivacaine in epidural analgesia for obstetrics Can Anaesth Soc J *16* 46 1969
5 Covino B G Comparative clinical pharmacology of local anesthetic agents Anesth *35* 158 1971
6 Doughty A Lumbar epidural analgesia The pursuit of perfection Anesthesia *30* 741 1975
7 Finster M Toxicity of local anesthetics in the fetus and newborn Bull N Y Acad Med *52* 222 1976
8 Greenhill J P & Friedman E A Biological principles and modern practice of obstetrics p 206 Saunders 1974
9 Steel C C & Dawkins C J M Extradural lumbar block with bupivacaine a clinical trial in lower abdominal and perineal surgery Anesthesia *23* 14 1968
10 Vasicka A & Kretchmer H E Uterine dynamics Clin Obstet Gynecol *4* 17 1961
11 Vasicka A & Kretchmer H The effect of conduction and inhalation anesthesia on uterine contractions Am J Obstet Gynecol 82 600 1961
12 Vasicka A Hutchinson H T Eng M Spinal and epidural anesthesia Fetal and uterine response to acute hypo and hypertension Am J Obstet Gynecol 90 800 1964

Submitted for publication July 27 1978

M L Tan er M D
Department of Obstetrics and Gynecology
The Brookdale Hospital Medical Center
Linden Bl d at Brookdale Plaza
Brooklyn NY 11212
USA

antibiotika

Acta Obstet Gynecol Scand 58 433–438 1979

AMNIOTIC FLUID PHOSPHATIDYLINOSITOL AND PHOSPHATIDYLGLYCEROL

II Diabetic and preeclamptic pregnancies

Julie Skjæraasen and S Stray Pedersen

From the Department of Obstetrics and Gynecology Rikshospitalet University of Oslo Oslo Norway

Abstract 139 samples of amniotic fluid from diabetic women collected during 34-39 weeks of pregnancy showed higher levels of lecithin phosphatidylinositol (PI) and phosphatidylglycerol (PG) indicating an accelerated surfactant synthesis as compared to that observed in normal pregnancies (13) In ten infants with respiratory distress syndrome (RDS) delivered from diabetic mothers the lecithin/sphingomyelin (L/S) PI/S and PG/S ratios were generally low Only four samples showed definitely immature L/S ratios whereas the amniotic fluid content of PG in all samples was unmeasurable or low

In 56 samples of amniotic fluid collected during the third trimester from preeclamptic pregnancies PI/S and PG/S ratios after 36-37 weeks were comparable with those of normal pregnancies In 11 neonates with subsequent RDS the L/S ratios were immature and PG was critically low or lacking in the majority of the samples

No convincing association between the PI content and development of RDS could be observed in any of the groups

Evidence has been collected suggesting that the increase in phosphatidylinositol (PI) and phosphatidyl glycerol (PG) in the amniotic fluid during the last weeks of pregnancies reflects the maturation of the surfactant system in the fetal lung (4 5 9 11 13) The occurrence of respiratory distress syndrome (RDS) in infants of diabetic mothers having adequate amniotic fluid lecithin concentrations has been assumed to be due to lack of PG (5 11) In cases of preeclampsia in the mother especially when combined with intrauterine growth retardation of the fetus RDS may not develop despite immature L/S ratios (12 14) This leads to the suggestion that the apparently decreased tendency to RDS in these infants might be ascribed to the presence of other phospholipids in the surfactant system such as for instance PI and PG

In the present study the amniotic fluid content of PI and PG in diabetic and preeclamptic pregnancies has been examined and compared with that measured in women with normal pregnancies (13) The concentrations of PI and PG in amniotic fluid from infants who contracted RDS were compared to those observed in neonates with no RDS

MATERIAL AND METHODS

Patients and sample collections The present study was based on phospholipid measurements in amniotic fluid from two different groups of patients at the Department of Obstetrics and Gynecology Rikshospitalet Oslo during the years 1974-1978

1 139 samples from 117 women with insulin-dependent diabetes
2 56 samples from 54 women with preeclampsia (i e blood pressure >140/90 proteinuria and edema) Five of their infants showed intrauterine growth retardation with birth weights below the 2 5 percentile (1)

Amniotic fluid was obtained by transabdominal amniocentesis by transuterine puncture at cesarean section or by puncture of the amniotic sac during vaginal delivery Samples grossly contaminated with blood or meconium were discarded

The results obtained in the two groups of abnormal pregnancies were compared to those observed in a previous study among normal pregnancies (13)

The phospholipid composition of the last amniotic fluid sample was related to the clinical outcome with respect to RDS in the infant Samples collected more than 1 week prior to delivery were considered as unreliable for this purpose The criteria used for the diagnosis of RDS were similar to those employed in earlier investigations (8)

Gestational age has in the text been given in weeks meaning completed weeks (i e 39 weeks = 273-279 days)

Phospholipid analyses The majority of the samples were analyzed immediately after the collection only a few samples were stored frozen at 20 C before they were examined The centrifugation the extraction of the phospholipids and the separation on thin layer chromatograms were performed as described previously (13)

Measurements of lipid phosphorus Sixty-one samples from 53 diabetic and 18 samples from 16 preeclamptic women were analyzed by two-dimensional thin-layer chromatography and the content of lipid phosphorus was determined in the different fractions (13)



antibioti
steroider



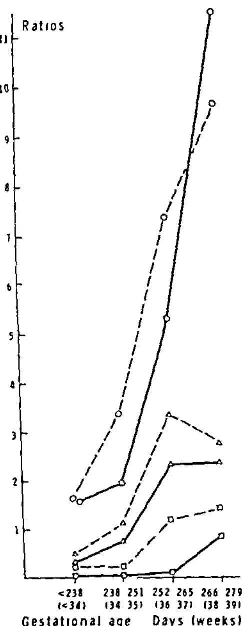


Fig 2 Diabetic pregnancies Median values of the chemically determined phospholipid ratios obtained in 61 samples from diabetic women and in 84 samples from normal pregnancies
○ L/S ratio △ PI/S ratio □ PG/S ratio — normal pregnancies -- diabetic pregnancies

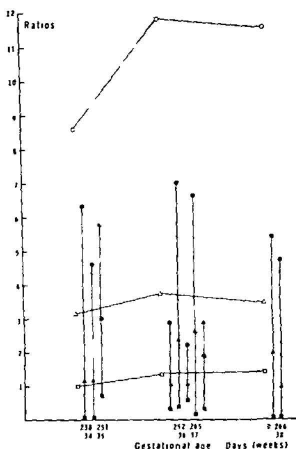


Fig 3 Diabetic pregnancies The individual phospholipid ratios chemically determined from 10 infants with RDS and the median values from 41 infants with no RDS
○ L/S ratio △ PI/S ratio □ PG ratio — median values
Filled symbols infants with RDS

with no RDS In only four cases the L/S ratios were immature (<4 5) indicating a high risk of RDS development The PI/S ratios were generally low except in one case but only marginally significantly different from the values observed in the samples from the non affected infants (p~0 05) As for PG/S the difference between the RDS and the non RDS infants was found to be highly significant (p<0 0001) In four among the ten cases PG could not be demonstrated and in another four cases the PG/S ratios were ≤0 4

Preeclamptic pregnancies The results obtained by the chemical and the densitometrical analyses of the 56 samples from the preeclamptic women are presented in Fig 4 The PI/S and PG/S ratios tended to be higher at gestational ages <36 weeks but after this stage of gestation they were comparable to the values observed in normal pregnancies

The chemically determined ratios in 16 infants of preeclamptic mothers are visualized in Fig 5 Only three of the infants developed RDS even though highly immature L/S ratios (≤3) could be observed in as

REFERENCES

1 Bjerkedal T Bakketeig L & Lehmann E H Percentiles of birth weights of single live births at different gestation periods Acta Pædiatr Scand *62* 449 1975
2 Gersony W M Persistence of fetal circulation A commentary J Pediatr *82* 1103 1973
3 Gluck L & Kulovich M Lecithin/sphingomyelin ratios in normal and abnormal pregnancy Am J Obstet Gynecol *115* 539 1973
4 Hallman M Kulovich M Kirkpatrick E Sugarman R G & Gluck L Phosphatidylinositol and phosphatidylglycerol in amniotic fluid Indices of lung maturity Am J Obstet Gynecol *125* 613 1976
5 Hallman M Feldman B H Kirkpatrick E & Gluck L Absence of phosphatidylglycerol (PG) in respiratory distress syndrome in the newborn Study of the M nor surfactant phospholipids in the newborns Pediat Res *11* 714 1977
6 Hallman M & Kankare P Respiratory distress syndrome (RDS) in offsprings of diabetic mothers due to the failure of surfactant phosphatidylglycerol (PG) induction *In* Abstract of 6th Nordic Congress of Perinatal Medicine Oulu Sept 1977
7 Jervell J Moe N & Bjerkedal T Outcome of pregnancies in diabetic mothers in Norway 1967 1976 To be published
8 Lindback T Frantz T Skjæraasen J & Graven S *Phospholipids in amniotic fluid Acta Obstet Gynecol* Scand *53* 219 1974
9 Rooney S A Canavan P M & Motoyama E K The identification of phosphatidylglycerol in the rat rabbit monkey and human lung Biochem Biophys Acta *360* 56 1974
10 Skjæraasen J & Lindback T Phospholipid concentrations in amniotic fluid from diabetic pregnant women *Acta Obstet Gynecol Scand 55 225 1976*
11 Skjæraasen J & Stray Pedersen S Phosphatidylinositol and phosphatidylglycerol in normal and in diabetic women *In* Abstract 6th Nordic Congress of Perinatal Medicine Oulu Sept 1977
12 Skjæraasen J Amniotic fluid phospholipid concentrations in pregnancies with preeclampsia and/or intrauterine growth retardation of the fetus Acta Obstet Gynecol Scand *58* 191 1979
13 Skjæraasen J & Stray Pedersen S Amniotic fluid phosphatidylinositol and phosphatidylglycerol I Normal pregnancies Acta Obstet Gynecol Scand *(In press)*
14 Usher R H Clinical and therapeutic aspects of fetal *malnutrition Pediatr Clin North Am 17 169 1970*

Submitted for publication Aug 3 1978

J Skjæraasen M D
Department of Obstetrics and Gynecology
Rikshospitalet
Oslo 5
Norway

Acta Obstet Gynecol Scand 58 439–442 1979

RATIO OF AMNIOTIC FLUID CORTISOL AND MATERNAL SERUM CORTISOL (AFC/MSC) AS AN INDEX OF FETAL LUNG MATURITY

K Varma M W Heine W S Haller A D Row K Railsback and S K Varma

From the Departments of Obstetrics and Gynecology Biochemistry and Pediatrics Texas Tech University School of Medicine Lubbock Texas U S A

Abstract Fifty-eight samples of amniotic fluid from pregnant women between the gestation period of 34-42 weeks were analyzed for total cortisol levels Thirty four simultaneous maternal serum total cortisol levels were also measured Amniotic fluid cortisol (AFC) maternal serum cortisol (MSC) and the ratio of AFC/MSC were correlated with L/S ratio AFC alone and AFC/MSC ratios correlate with L/S ratios (r=0 36 $p<0$ 01 and r=0 46 $p<0$ 01 respectively) MSC and L/S ratios had no correlation AFC/MSC had less individual variation as compared to AFC alone The AFC/MSC had less individual variation as compared to AFC alone The AFC/MSC could be divided by an arbitrary line at 0 1 and values less than 0 1 signify immature fetal lungs Values of 0 1 and greater signify *mature fetal lungs*

Measurement of amniotic fluid cortisol (AFC) has been done by many investigators in the past (2 4 5 10 11 12) Some of these investigators (2 11 12) have tried to correlate AFC with L/S ratio in order to assess it as an index of fetal lung maturation in clinical follow up of obstetric patients as well as its physiological role in fetal lung maturation However due to wide variability in the results from various investigators the reports are not conclusive One of the possible causes could be fluctuations in the cortisol values because of time and stress due to fear and anxiety These factors are known (8 9) to affect the serum cortisol and there is a possibility of the same factors existing in the amniotic fluid cortisol as well It is not a practical possibility to study this in humans by doing multiple amniocentesis but a simple attempt was made here to study the amniotic fluid cortisol/maternal serum cortisol (AFC/MSC) ratio and to correlate it with L/S ratio as well as to study the correlation of AFC and MSC with L/S ratio separately and see if AFC/MSC ratio is a better index of fetal lung maturity

MATERIAL AND METHODS

Fifty eight pregnant women of normal as well as abnormal pregnancy were selected from the patients attending the Obstetrics Clinic at the Texas Tech University School of Medicine and from the local private physicians clinics These patients were from 34-42 weeks of gestation calculated from the first day of the last menstrual period Amniotic fluid was obtained by transabdominal amniocentesis

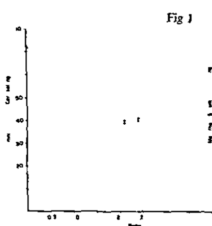


Fig 1

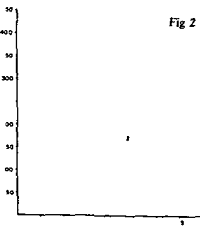


Fig 2

Fig 1 Amniotic fluid cortisol (AFC) ng/ml against L/S ratio

Fig 2 Maternal serum cortisol (MSC) ng/ml against L/S ratio

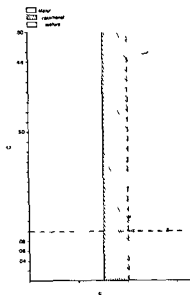


Fig 3 Ratio of amniotic fluid cortisol/maternal serum corti sol (AFC/MSC) against L/S ratio

None of the patients were in labor at the time of sample col lection All specimens were stored at 20 C until assayed Samples with muconeum or with blood were discarded Thirty four specimens of maternal blood were collected within 30 minutes after amniocentesis Serum was separated and kept frozen at 20 C until assayed Total cortisol in am niotic fluid and maternal serum were measured by cortisol radioimmunoassay kit from Micromedics (7) The ssay coefficient of variation of cortisol concentration per cent The inter assay coefficient of variation was cent L/S ratio was determined by the method of and associates (6) Variances are expresssed as ± one andard deviation of the mean for statistical analysis The coefficient of correlation between the amniotı fluid cortisol and L/S ratio and between maternal serum cortisol and L/S ratio were estimated by linear regression analysis r P value of <0 05 was considered significant

Table I *Comparison of individual AFC/MSC ratio less than 0 1 with L/S ratio (Group A)*

Patient No	AFC/MSC	L/S
1	0 03	1 6
2	0 05	1 3
3	0 09	2 2
4	0 09	1 4
5	0 08	1 4
6	0 08	2 3
7	0 04	1 3
8	0 07	1 0
9	0 08	1 4

Table II *Comparison of individual AFC/MSC ratio 0 1 or more with L/S ratio (Group B)*

Patient No	AFC/MSC	L/S
1	0 21	2 4
2	0 14	2 3
3	0 45	3 2
4	0 10	2 1
5	0 22	2 1
6	0 13	2 0
7	0 14	3 0
8	0 13	2 4
9	0 22	2 7
10	0 10	2 8
11	0 30	1 9
12	0 11	2 3
13	0 23	2 4
14	0 13	2 0
15	0 34	2 3
16	0 15	2 1
17	0 11	2 5
18	0 10	2 8
19	0 12	2 4
20	0 19	2 6
21	0 11	2 5
22	0 10	2 1
23	0 26	0 5
24	0 12	3 2
25	0 11	1 7

RESULTS

Measurement of AFC in 58 patients showed wide variation as shown in Fig 1 AFC varied from 6 ng/ml to 108 ng/ml with a mean (±S D) of 34 5±17 5 ng/ml Its correlation with L/S ratio was significant ($r=0$ 36 $p<0$ 01)

The cortisol measurement in 34 maternal sera (MSC) as shown in Fig 2 also had wide range vary ing from 93 to 400 ng/ml with a mean (±S D) of 226 5±84 6 ng/ml Its correlation with L/S ratio was not significant

A ratio of AFC/MSC as shown in Fig 3 seems to have lesser wide range varying from 0 03 to 0 4 with a mean (±S D) of 0 14±0 09 Its correlation with L/S ratio was significant ($r=0$ 46 $p<0$ 01)

The individual results of AFC/MSC ratio have been divided into two subgroups A and B by an ar bitrary line at 0 1 Group A (Table I) had nine pa tients with AFC/MSC ratio of less than 0 1 while Group B (Table II) had 25 patients with AFC/MSC ratio of 0 1 or more Out of nine patients in Group A (Table I) seven had L/S ratio of less than 2 while two had L/S ratio of more than 2 In Group B (Tabl II) 22 of 25 patients had L/S ratio of 2 or more At this point no attempt had been made to correlate it with fetal outcome or to separate the normal and ab normal pregnancy

Table III *Comparison of present results with other investigators*

No	Investigator	AFC Mean±SD	MSC Mean±SD	AFC/MSC Mean±SD	No of patients	Types of pregnancy	Weeks of gestation	L/S correlation
I	Fencl & Tulchinsky Jan 1975	72 4± 3 8			43	Normal	34–40	r=0 83 ($p<0\ 001$)
II	Sivakumaran *et al* June 1975	202 0±95 0			45	Normal & complicated	37–40	Not significant
III	Tan *et al* Jan 1976	19 8± 1 5				Complicated	30–40	r=0 36 ($p<0\ 005$)
IV	Present	34 5±17 5			58	Normal & complicated	34–42	r=0 36 ($p<0\ 01$)
			226 5±84 6		34	Normal & complicated	34–42	Not significant
				0 14±0 09	34	Normal & complicated	34–42	r=0 46 ($p<0\ 01$)

AFC and MSC valu s gi en in ng/ml

with fetal outcome or to separate the normal and ab normal pregnancy

DISCUSSION

A summary of the results of previous investigations as well as present work is given in Table III The pres ent result of correlation of AFC and L/S ratio is com parable to other investigators (2 11 12) Although it has a significant correlation with L/S ratio the in dividual wide variability has made it clinically inap plicable The same wide variability has been obtained by Sivakumaran *et al* (11)

MSC has no significant correlation with L/S ratio The ratio of AFC/MSC statistically has the same sig nificant correlation as AFC with L/S ratio but the individual variations are less The arbitrary division at 0 1 could be used as a clinical tool along with other parameters to signify mature or immature fetal lungs (i e values of AFC/MSC less than 0 1 signify im mature fetal lungs and values of 0 1 and greater signify mature fetal lungs)

One can question at this point how the fluctuations in maternal serum cortisol are going to affect the am niotic fluid cortisol when amniotic fluid is supposed to be fetal in origin in the latter part of gestation (1 3) But no one can say that maternal status does not affect the fetus and thereby the amniotic fluid However th study included a small number of pa tients and further studies are needed in order to assess whether or not the ratio of AFC/MSC can be used as an index of fetal lung maturity in clinical manage ment of patients The test itself is less time consum ing easy to set up and comparatively inexpensive

ACKNOWLEDGEMENTS

The authors wish to acknowledge the cooperation of the staff and nurses of St Mary of the Plains Hospital and the physicians of the women s Clinic and Doctors DeShan Hinz Filippone and R Misenhimer

REFERENCES

1 Alexander D P Nixon D A Widdar W F & Howlzogen F X Renal function in sheep foetus J Physiol *140* 14 1958
2 Fencl M D & Tulchinsky D Total cortisol in am niotic fluid and fetal lung maturation N Engl J Med *292* 113 1975
3 Fencl M D Osathanondh R & Tulchinsky D Plasma cortisol and cortisone in pregnancies with nor mal and anencephalic fetuses J Clin Endocr Metab *43* 80 1976
4 Gewolb I H Hobbins J C & Tan S Y Amniotic fluid cortisol as an index of fetal lung maturity Obstet Gynecol *49* 462 1977
5 Gewolb I H Hobbins J C & Tan S Y Amniotic fluid cortisol in high risk human pregnancies Obstet Gynecol *49* 466 1977
6 Gluck L Kulovich M V Borer R C Brenner P H Anderson C G & Spellacy W N The diagnosis of respiratory distress syndrome (RDS) by am niocentesis Am J Obstet Gynecol *109* 440 1971
7 Hasler M J Painter K & Niswender G D An I labeled cortisol radioimmunoassay in which serum binding proteins are enzymatically denatured Clin Chem *22* 1850 1976

8 Perkoff G T Eik Nes K Nugent C A Fred H L Nimer R A Rush L Samuels L T Tyler F H Studies of the diurnal variation of plasma 17 hydroxycorticosteroids in man J Clin Endocrinol and Metab *19* 432 1959
9 Pincus G A diurnal rhythm in the excretion of urinary ketosteroids by young men J Clin Endocrinol *3* 195 1943
10 Sharp Cageorge S M Blicher B N Gordon E R & Murphy B E P Amniotic fluid cortisol and human fetal lung maturation N Engl J Med *296* 89 1977
11 Sivakumaran T Duncan M L Effer S B & Younglai E V Relationship between cortisol and lecithin/sphingomyelin ratios in human amniotic fluid Am J Obstet Gynecol *122* 291 1975
12 Tan S Y Gewolb I H & Hobbins J C Unconjugated cortisol in human amniotic fluid relationship to lecithin/sphingomyelin ratio J Clin Endocrinol and Metab *43* 412 1976

Submitted for publication January 11 1978

K Varma M D
Department of Obstetrics and Gynecology
Texas Tech University
Health Sciences Centers
School of Medicine
Lubbock Texas 79430
U S A

Acta Obstet Gynecol Scand 58 443–445 1979

CIRCULATORY AND METABOLIC EFFECTS OF ACUTE BETA$_1$ BLOCKADE IN SEVERE PRE ECLAMPSIA

N O Lunell B Persson G Aragon B B Fredholm and H Aström

From the Department of Obstetrics and Gynecology Karolinska Institutet Huddinge University Hospital and Phillipine General University Hospital Manila The Phillipines Department of Pediatrics Karolinska Institutet St Göran s Hospital Department of Pharmacology Karolinska Institutet and Department of Physiology Karolinska Institutet Huddinge University Hospital Stockholm Sweden

Abstract Five mg of a beta$_1$ adrenoceptor antagonist (atenolol) was given i v to 5 women with severe pre eclampsia in the 3rd trimester of pregnancy There was a significant decrease of both mean systolic blood pressure from 171 to 155 mm Hg and mean diastolic blood pressure from 116 to 107 mm Hg The mean maternal heart rate decreased significantly from 90 to 74 and mean fetal heart rate significantly from 145 to 138 beats per min There were no significant changes in the plasma levels of cyclic AMP insulin glucose free fatty acids 3 hydroxy butyrate or glycerol

Beta blocking agents are widely used in the treatment of essential hypertension Due to their depressive action on the fetus (6 3) and their effects on uterine activity (1) the non elective beta blocking agents have not come into common use in the treatment of pre eclampsia

A cardio selective beta blocker with reduced effect on beta$_2$-adrenoceptors could be advantageous in the treatment of pre-eclampsia Of these compounds atenolol might offer particular advantages since little of radioactive atenolol given to pregnant rats was detected in the fetus (11) We have therefore studied the acute effects of antenolol on patients with pre eclampsia with regard to maternal blood pressure response maternal and fetal heart rate and maternal plasma levels of glucose insulin glycerol 3 hydroxy butyrate free fatty acids (FFA) and cyclic AMP

MATERIAL AND METHODS

Five women with severe pre-eclampsia were studied (Table I) Three of them (AT LG AL) were treated with 5 10 g $MgSO_4$ 50 mg pethidine and 25 mg promethazine 1-6 hours before atenolol was given Five mg of atenolol was injected i v in divided doses over a 20 min period No side-effects were observed Maternal and fetal heart rates were recorded every 10 min and blood samples were collected at −20 0 20 40 and 60 min in chilled heparinized tubes After centrifugation plasma was stored frozen until analysed All analyses were performed in duplicate Glucose was determined with a glucose-oxidase method (Glox AB Kabi Sweden) glycerol fluorimetrically (8) FFA colometrically (9) 3 hydroxy butyrate enzymatically (10) insulin by radioimmunoassay (Phadebas[R] Pharmacia Sweden) Cyclic AMP was determined according to the method of Brown *et al* (1972) with modifications (5)

RESULTS

Following 5 mg atenolol i v there was a significant fall in mean diastolic blood pressure from 116±9 to 107±10 (SD) mm Hg ($p<0.05$) (Fig 1) The mean systolic blood pressure fell from 171±15 to 155±12 mm Hg the decrease being significant after 50 min ($p<0.02$) Mean maternal heart rate showed a significant fall already after 10 min ($p<0.01$) The total decrease was from 90±10 to 74±9 beats per min (Fig 1) Mean feteal heart rate showed a maximal decrease from 145±9 to 138±8 beats per min which was significant after 20 min ($p<0.02$) Plasma concentrations of glucose insulin FFA glycerol 3 hydroxy butyrate and cyclic AMP showed only insignificant changes (Fig 2)

DISCUSSION

Beta mimetic drugs are currently used in obstetrics to treat threatened premature labor The inhibition of uterine activity is accompanied however by other undesireable effects of the beta adrenergic drug the most evident being those from the cardiovascular beta receptor like tachycardia and palpitation It would be desireable to block these cardiac effects and still maintain the effect on the uterine beta receptors The cardioselective beta adrenoceptor antagonist

Table I *Clinical data of patients with pre eclampsia*

Mother							Infant			
								Birth		
Subject	Age (years)	Grav / para	Gest age (weeks)	Basal blood pressure mm Hg	Edema	Protein uria	Sex	weight (g)	length (cm)	Apgar 1 /5
PD	36	5/4	36	180/110	–	–	F	2 295	45	10/10
							M	2 375	48	10/10
AT	21	1/10	40	160/110	+	–	F	2 960	48	10/10
DA	20	1/0	36	170/110	+	–	M	2 850	49	10/10
LG	26	1/0	35	190/130	+	+	M	2 040	44	7/10
AL	17	3/0	37	160/110	+	–	F	2 370	46	8/10

in labor

practolol has been shown to block the cardiac effect of a beta stimulating drug without blocking its in hibiting effect on the uterus (2 4) However practolol cannot be used in chronic treatment because of its muco cutaneous side effects

Beta blockade of the fetus would be undesireable It has been shown that beta blocking drugs which cross the placenta are more soluble in organic solvents than those which did not cross the placenta (12) Atenolol has a low lipid solubility compared to propranolol (11) Consequently it would not pass across the placenta so rapidly which could be a desireable property when treating pregnant women It is not known however whether there is any real difference in the steady state fetal level of the drugs long term treatment Acute administration of l reduced the maternal heart rate by about 20 in accordance with acute studies in non humans when atenolol was given in the same dose range (13) There was however only a 5 per cent decrease in the fetal heart rate which could indicate a lower concentration and/or a lower re sponsiveness of atenolol at the beta receptors of the fetal heart There was also a decrease in blood pres sure within 10-20 min along with the reduction in heart rate

The newborn infants were not adversely affected by the atenolol, as judged from Apgar scores at 1 and 5 min

Atenolol did not induce any significant acute changes in carbohydrate and lipid metabolism or cyclic AMP Lack of significant metabolic side effects would be an important advantage during treatment of pre eclampsia but it is not known whether metabolic disturbances develop when drug treatment is extended

In conclusion the present data show that acute ad ministration of atenolol reduces maternal blood pressure and heart rate with minimal effects on the fetus and on various metabolic parameters These en couraging results make a study of the actions of atenolol over the longer term highly desireable

ACKNOWLEDGEMENTS

This study was supported by grants from the Swedish Medical Research Council (Proj no 04X 4553 19P-4106 19X-03787) Tielman s Fund for Paediatric Research Expressen s Fund for Paediatric Research and by Stiftelsen Allmänna Barnbördshusets Minnesfond

REFERENCES

1 Barden T P & Stander R W Myometrial and cardiovascular effcts of an adrenergic blocking drug in human pregnancy Am J Obstet Gynecol *101* 91 1968

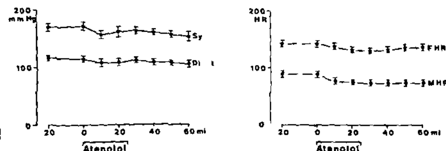


Fig 1 Changes in maternal blood pressure and maternal (MHR) and fetal (FHR) heart rates after 5 mg of atenolol

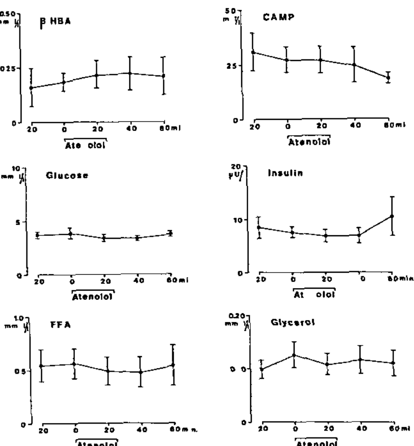


Fig 2 Plasma levels of glucose insulin free fatty acids (FFA) glycerol 3 hydroxy butyrate (β HBA) and cyclic AMP (CAMP) after 5 mg of atenolol

2 Beveridge H & Wood C Du 21220 A new Beta mimeti drug A pilot trial to determine its use as a uterine relaxant in conjuction with the Beta blocking drug practolol Aust NZJ Obstet Gynaec *10* 252 1970
3 Cottrill C M McAllister R G Gettes L & Noonan J A Propranolol therapy during pregnancy labor and delivery Evidence for transplacental drug transfer and impaired neonatal drug disposition J Pediatrics *91* 812 1977
4 Esteban Alturriba J René A M J Duran P Cabero L Giralt E Carteras M & Garcia Cambronere M T An attempt at blocking the car diovascular and metabolic side effects of beta mimetic drugs during labor J Perinat Med *2* 243 1974
5 Fredholm B B Lunell N O Persson & Wager J Actions of salbutamol in late pregnancy Plasma cyclic AMP insulin and C peptide carbohydrate and lipid metabolites in diabetic and non-diabetic women Diabetologica *14* 1 1978
6 Gladstone G R Hordof A & Gersony W M Propranol administration during pregnancy Effects on the fetus J Pediatrics *36* 962 1974
7 Hansson L Beta adrenergic blockade in essential hypertension Effects of propranol on haemodynamic parameters and plasma renin activity Acta Med Scand Suppl 550 1973
8 Laurell S & Tibbling G An enzymatic fluorometric micromethod for the determination of glycerol Clin Chim Acta *13* 317 1966
9 Laurell S & Tibbling G Colormetric microdeter mination of free fatty acids in plasma Clin Chim Acta *16* 57 1967
10 Persson B Determination of plasma acetoacetate and D β hydroxy butyrate in newborn infants by an en zymatic fluorometric micromethod Scand J Clin Lab Invest *25* 9 1969
11 Snowden N & Langshow N ICI report 1976
12 Truelove J F von Petten G R & Willes R F Action of several Beta adrenoceptor blocking drugs in the pregnant sheep and foetus Br J Pharmac *47* 161 1973
13 Åström H & Vallin H Effect of a new beta adrenergic blocking agent ICI 66082 on exercise haemodynamics and airways resistance in angina pectoris Brit Heart J *36* 1194 1974

Submitted for publication June 12 1978

N O Lunell M D
Department of Obstetrics and Gynecology
Huddinge University Hospital
S-141 86 Huddinge
Sweden

Nyregistrerat

Acta Obstet Gynecol Scand 58 447–451 1979

EFFECT OF LONG TERM SALBUTAMOL TREATMENT ON RENIN ALDOSTERONE SYSTEM IN TWIN PREGNANCY

R Lammintausta and R Erkkola

From the Department of Pharmacology the Institute of Biomedicine University of Turku and the Department of Obstetrics and Gynecology University Central Hospital Turku Finland

Abstract Plasma renin activity (PRA) urinary aldosterone excretion (dU Aldo) urinary electrolytes (dU Na dU K) and plasma progesterone were studied weekly in 22 women with twin pregnancies for three weeks whilst on salbutamol therapy (=8 mg three times daily) in hospital Fifteen patients in this group were treated with diuretics for on an average six weeks and the therapy continued All the patients except three were treated also with depot formed oxyprogesterone during the study As an additional control group ten twin pregnant women without any drug therapies were studied

The mean level of PRA in twin pregnancy before betasympathomimetics was equal to that of the same phase (the 32nd week) of normal pregnancy On the second day of the treatment the PRA levels was threefold ($p<0$ 001) and later on twofold ($p<0$ 05) when compared with the level before the treatment

Before betasympathomimetics the mean level of dU Aldo was in twin pregnancy already higher than in normal pregnancy ($p<0$ 01) During the treatment dU Aldo increased within a week ($p<0$ 05 $p<0$ 01) and a positive correlation between PRA and dU Aldo was found ($p<0$ 01) A decrease in dU Na and an increase in dU K were found ($p<0$ 05) corresponding to the increased effect of aldosterone The increased levels of progesterone and aldosterone in twin pregnancy agree with earlier suggestions concerning the importance of progesterone in the secretion of aldosterone during pregnancy The stimulating effect of betasympathomimetics however leads to a renin mediated secondary aldosteronism and therefore tend also to cause hypokalemia

Normal pregnancy is associated with a highly activated renin angiotensin system and with high aldosterone secretion (5) The basal level of PRA during pregnancy even exceeds the stimulatory reserves of the non pregnant state therefore in addition to the kidney an uteroplacental or chorionic site of renin production is suggested (4 6) Twin pregnancy has more chorionic and placental tissue than a singleton pregnancy and pre-eclamptic toxemia with circulatory disorders is more frequent and severe (12) The high rate of preterm labors leads to frequent medical treatment during twin pregnancy especially with tocolytics and diuretics

During pregnancy diuretic treatment leads to a strong compensatory activation of the renin angiotensin system to an increased PRA and to obvious secondary aldosteronism (7) Beta sympathomimetic

Table 1 *Presentation of the patients with twin pregnancy*

	Group A (10)	Group B (1)	Group C (10)
Maternal age (years)			
(mean±SEM)	25 9±1 7	28 1±0 8	26 2±2 0
range	19–35	24–32	21–31
Prepregnant weight (kg)	68 2±2 6	75 5±3 0	69 0±3 2
range	49–77	63–95	54–78
Weight gain (kg)	12 6±1 3	12 3±1 9	11 4±1 6
range	6–18	0–19	7–15
Week of hospitalization	3 ±0 3	31 8±0 3	32 2±0 3
range	30–33	30–33	30–33
Week of delivery	35 6±0 2	36 3±0 5	36 8±0 4
range	34–36	35–38	35–38
Weight of baby A (g)	2514±7	670±108	2720±98
Weight of baby B (g)	2574±64	?680±180	2743±105
Weight of placenta (g)	816±33	824±49	834±52

The figures w th n parenthesis denote n mber of patients

Table II *The mean levels of PRA (±SEM) in twin pregnant patients during the salbutamol treatment*

Days of treatment	PRA (ng/ml×h) Group A	Group B	Group C
0	15 9±3 7 (10)		13 6±2 5 (10)
2		48 9±6 4 (12)	
7	27 6±3 3 (9)	33 2±6 5 (11)	
14	31 7±3 9 (8)	35 1±8 3 (11)	
21	22 1±4 2 (4)	26 7±3 9 (11)	

The figures within parenthesis denote number of patients

tocolytics are able to double the level of PRA during infusion therapy (8)

This study was carried out to demonstrate the basal levels of PRA and aldosterone excretion in twin pregnancy and to follow the long term effects of salbutamol during conventional prophylactic treatment

SUBJECTS AND METHODS

The study comprised 32 women with twin pregnancies They were hospitalized for observation at about the 32nd week of pregnancy In hospital 22 of them were treated with salbutamol tablets (Ventoline[R] Glaxo England or Salbumol[R] Medica Finland) 8 mg three times daily for prophylaxis of the preterm labor In addition 19 of the women were treated with 17α hydroxyprogesterone caproate (oxyprogesterone) (Primolut Depot[R] Leiras Finland) 250 mg weekly intramuscularly Before hospitalization 15 patients had received chlorthiazide therapy (500 mg daily) for an age of six weeks The diuretic therapy was continued ged During the study in hospital plasma renin activ A) plasma progesterone (P Prog) 24 h urinary excretion of aldosterone (dU Aldo) sodium (dU Na) and potassium (dU K) were studied weekly Because all the patients could not be included in the study before the salbutamol treatment the patients treated are presented in two separate groups

Group A consisted of 10 patients who were studied prior to and following 7 14 and 21 days salbutamol therapy Six of them were receiving diuretic therapy and nine patients were given oxyprogesterone

Group B (n = 12) was studied after 2 7 14 and 21 days salbutamol therapy Nine patients were taking diuretic therapy and ten were receiving oxyprogesterone

Ten women with twin pregnancies and without any drugs administered were studied in hospital once on the 30th to 33rd weeks for further control (Group C)

Table I lists the maternal age prepregnant weight weight gain the week of hospitalization the week of delivery and the weights of the babies and the placenta in the study groups

Blood samples for the estimation of PRA and P Prog were withdrawn at noon after ambulation in the Department The sample for PRA was taken into a chilled EDTA tube in ice water separated in 10 min by a refrigerated centrifuge and stored frozen For the estimation of PRA the angiotensin I generated by plasma renin in 1 h at pH 6 0 was determinated by radioimmunoassay and expressed as ng/ml

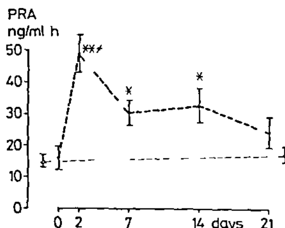


Fig 1 Mean (±SEM) levels of PRA during salbutamol therapy in twin pregnancy The triangels signify the level for normal pregnancy at 30 and 34 weeks gestation compared with the pretreatment level
 = $p<0\ 05$ = $p<0\ 01$ ** = $p<0\ 001$

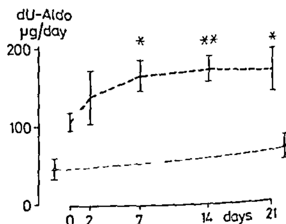


Fig 2 Mean (±SEM) levels of urinary aldosterone excretion (dU Aldo) during salbutamol therapy Abbreviations as in Fig 1

Table III *The mean levels of urinary aldosterone excretion (dU Aldo) (±SEM) in twin pregnant patients during the salbutamol treatment*

Days of treatment	dU Aldo (µg/day) Group A	Group B	Group C
0	108±13 (9)		112±12 (10)
2		141±25 (4)	
7	172±32 (9)	157±18 (5)	
14	168±30 (7)	182±33 (6)	
21	172±26 (4)	171±42 (4)	

The figures within parentheses denote number of patients

×h (5) The labelled angiotensin I and the antiserum were obtained from Oy Medix Ab Finland P Prog was determined by radioimmunoassay (2)

For dU Aldo a 24-hour urine was collected starting 7 a m the free and acid labile glucuronized aldosterone in urine were determined by radioimmunoassay after a chromatographic purification (5) Sodium and potassium were measured by atomic absorption spectrophotometer

For statistical evaluation the Student s t tests for two means and for paired data were used

RESULTS

Plasma renin activity (Table II Fig 1)

In Group A PRA increased during the 7 days of salbutamol therapy ($p<0.05$) and the higher level was maintained until 21 days In Group B the level of PRA on the 2nd day was already higher than before

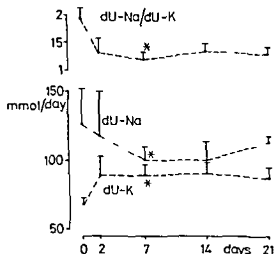


Fig 3 Mean (±SEM) levels of urinary sodium (dU Na) potassium (dU K) and sodium potassium ratio (dU Na/dU K) during salbutamol therapy Abbreviations as Fig 1

or on the 7th day of salbutamol in Group A ($p<0.001$ and $p<0.05$ respectively) In Group B PRA then decreased during the treatment between the 2nd and 7th day ($p<0.05$) The level of PRA was equal on 7th treatment day in Groups A and B During the subsequent two weeks no difference could be found in the PRA level between the two groups either or within the groups On the basis of the similarity of the groups on the 7th to 21st day a combined profile for PRA during salbutamol therapy is presented in Fig 1 No difference was found in PRA between Group A before salbutamol and Group C

Aldosterone (Table III Fig 2) In Group A the urinary excretion of aldosterone was increased by seven days during salbutamol treatment ($p<0.05$) but for the subsequent two weeks the level remained unchanged In Group B no change was seen in dU Aldo during treatment From the 7th to the 21st day of the study there was no difference in dU Aldo between the groups We have thus combined the groups A and B in Fig 2 The profile indicates that salbutamol treatment induced an increase in aldosterone excretion by seven days ($p<0.05$) and the level was higher also at the 14th and 21st day than before the treatment ($p<0.01$ and $p<0.05$ respectively) A positive linear correlation was found between PRA and dU Aldo ($n=59$ $r=0.40$ $p<0.01$)

Sodium and potassium (Table IV Fig 3) No changes or differences between the groups were found When combining the groups A and B the dU Na decreased between day 0 and 7 ($p<0.05$) (Fig 3) while dU K increased by seven days treatment ($p<0.05$) Between dU Aldo and dU K during the study a positive linear correlation was found ($n=43$ $r=0.39$ $p<0.01$)

Progesterone (Table V) No significant changes were found in the mean level of plasma progesterone during the treatment and no correlation could be demonstrated either between P Prog and dU Aldo

Table IV *The mean levels (±SEM) of urinary sodium (dU Na) and potassium excretions (dU K) and the ratio (dU Na/dU K) in twin pregnant patients during the salbutamol treatment)*

	dU Na mMol/day		dU K (mmol/day)		dU Na/dU K	
Days of treatment	Group A	Group B	Group A	Group B	Group A	Group B
0	127±30 (9)		69±5 (9)		1 9±0 4 (9)	
2		119±30 (4)		90±18 (4)		1 3±0 3 (4)
7	100±12 (9)	104±16 (5)	82±7 (9)	108±20 (5)	1 3±0 2 (9)	1 0±0 1 (5)
14	97±16 (7)	111±23 (6)	85±6 (7)	99±16 (6)	1 3±0 2 (7)	1 3±0 4 (6)
21	116± 5 (4)	109±11 (4)	89±7 (4)	98±10 (4)	1 3±0 1 (4)	1 0±0 1 (4)

The figures w thin parenthesis denote number of patients

levels or between P Prog and PRA during the study

To determine the effect of the diuretic and oxypro gesterone therapies on PRA and dU Aldo during the study period we listed the PRA and dU Aldo levels before and on the 7th day of salbutamol therapy (Table VI) No significant differences could be found

DISCUSSION

In twin pregnancy before the betasympathomimetic therapy the urinary aldosterone excretion was higher than in our earlier study of normal pregnancy ($p<0\ 01$) (5) while PRA did not differ significantly from the normal pregnancy level The study group of pregnancy included patients with diuretic thera singleton pregnancy at the same phase the ic therapy doubles the PRA and dU Aldo lev in one week (7) The high level of dU Aldo found in this study can not be merely secondary one to the diuretic therapy because no difference was found be tween the patients on diuretic therapy and those with out it There must be other factors which increase the aldosterone in twin pregnancy The role of the uteroplacental unit in aldosterone synthesis is unknown whereas on the other hand progesterone

Table V *The mean levels (±SEM) of plasma proges terone (P Prog) in twin pregnant patients during the salbutamol treatment*

Days of treatment	P Prog (mmol/l)
0	811±108 (8)
2	600±67 (8)
7	798±78 (8)
14	699±62 (6)
21	873±122 (9)

The figures within parenthesis denote number of patients

has been thought to play a significant role in the in creased aldosterone secretion during pregnancy (10) In our patients with twin pregnancies the mean plasma progesterone level was near by doubled in comparison with the level of normal pregnancy at the same phase and with the same method of assay (1) The natriuretic effect of progesterone may require a compensatory increase of aldosterone secretion In relation to the level of dU Aldo the basal level of PRA was lower in twin pregnancy than in normal pregnancy The reaction of PRA to the diuretic thera py seems also low A lower than normal PRA is as sociated with the toxemic disorders in pregnancy (3 14) The twin pregnancy with a high progesterone and aldosterone but with normal pregnant PRA levels is in accordance with our earlier suggestion about the autonomous increase of the basal aldosterone secre tion during pregnancy (5) Aldosterone can have a suppressive effect on PRA like in the primary aldosteronism

The depot formed oxyprogesterone administered during the study and thought to have a gestagenic significance in pregnancy did not possess any discer nible effect on aldosterone excretion according to the results of this study This is quite conceivable because 17α OH progesterone like certain other syn thetic progestagens is devoid of natriuretic effect as shown by earlier studies (9 11)

The increase of PRA after two days salbutamol treatment in twin pregnancy is of the magnitude found during infusions of isoxsuprine or ritodrine in normal pregnancy (8) The correlation between the PRA and aldosterone values seems to indicate that renin acts as a mediator in aldosterone secretion dur ing sympathomimetic therapy Betamimetics are found to cause hypokalemia within only a few hours during the infusion (13) During this short term treat ment however no increase in potassium excretion

Table VI *Mean levels (±SEM) of PRA and dU Aldo in twin pregnant patients with and without oxyprogesterone (= no treatment or more than 5 days from the last dose) and with and without diuretic treatment*

	PRA (ng/ml×h)	dU Aldo (μg/day)
Before salbutamol		
on oxyprogesterone	10±2 (4)	121±18 (4)
no oxyprogesterone	16±4 (16)	107±14 (15)
The 7th day on salbutamol		
on oxyprogesterone	33±7 (11)	182±34 (6)
no oxyprogesterone	26±5 (9)	158±20 (8)
Before salbutamol		
on diuretics	21±5 (6)	108±13 (5)
no diuretics	12±3 (14)	110±17 (14)
The 7th day on salbutamol		
on diuretics	33±5 (13)	174±26 (9)
no diuretics	31±7 (7)	152±30 (5)

The figures with parenthesis denote number of patients

was found as in this study during one week In this study the changes in sodium and potassium excretions reflect an increased effect of aldosterone In the long term use the secondary aldosteronism can provoke a positive sodium balance and hypokalemia Because it can be combined with diuretics the *betasympathomimetic therapy may exacerbate the* previous secondary aldosteronism leading to an abolition of the diuretic effect and to potentiation of the hypokalemic effect

ACKNOWLEDGEMENTS

This study was partly supported by the Lääke Medipolar Research Foundation

REFERENCES

1 Csapo A I & Pulkkinen M Unpublished work cited by Csapo A I in The Fetus and Birth Ciba found Symp 47 (new series) p 187 1977
2 De Villa G D Roberts K Wiest W G Mikhail G & Flickinger G A specific radioimmunoassay of plasma progesterone J Clin Endocrinol Metab *35* 458 1972
3 Editorial Progress in pre-eclampsia Lancet *I* 754 1973
4 Kokot F & Cekanski A Plasma *renin activity in* peripheral and uterine vein blood in pregnant and non pregnant women Am J Obstet Gynecol 79 72 1972
5 Lammintausta R & Erkkola R Renin angiotensin aldosterone system and sodium in normal pregnancy a longitudinal study Acta Obstet Gynecol Scand *56* 221 1977
6 Lammintausta R Eronen M & Erkkola R The effect of normal labor on the renin angiotensin system in mother and fetus Am J Obstet Gynecol *127* 390 1977
7 Lammintausta R Erkkola R & Eronen M Effect of chlorthiazide treatment on renin aldosterone system during pregnancy Acta Obstet Gynecol Scand *57* 389 1978
8 Lammintausta R Erkkola R & Kataınen P Effect of infused betamimetics on plasma renin activity during pregnancy Brit J Obstet Gynaecol *85* 828 1978
9 Landau R L Lugibihl K & Dimick D F Metabolic effects in man of steroids with progestational activity Ann NY Acad Sci *71* 588 1958
10 Ledoux F Genest J Nowaczynski W Kuchel O & Lebel M Plasma progesterone and aldosterone in pregnancy Can Med Assoc J *112* 943 1975
11 Oelkers W Schöneshöfer M & Blümel A Effects of progesterone and four synthetic progestagens on sodium balance and the renin aldosterone system in man J Clin Endocrinol Metab *39* 882 1974
12 Schmid Tannwald I & Hauser G A Incidence and forms of EPH gestosis in twin pregnancy Isr J Med Sci *12* 231 1976
13 Smith S K & Thompson D The effect of intravenous salbutamol upon plasma and urinary potassium during premature labor Br J Obstet Gynecol *84* 344 1977
14 Weir R J Brown J J Fraser R Kraszewski A Lever A F McIlvaine G M Morton J J Robertson J I S & Tree M Plasma renin renin substrate angiotensin II and aldosterone in hypertensive disease of pregnancy Lancet *I* 291 1973

Submitted for publication April 24 1978

Risto Lammintausta M D
Department of Pharmacology
University of Turku
Kiinamyllynkatu 10
05 0 Turku 52
Finland

ANNOUNCEMENT

The Center for Disease Control the International Union Against the Venereal Diseases and Treponematoses and other national and international agencies are sponsoring an **International Symposium on Pelvic Inflammatory Disease (PID)** on April 1 3 1980 in Atlanta Georgia Scientific papers will be presented on clinical and laboratory aspects of diagnosis management and the epidemiology management and control of PID

Abstracts Abstracts related to the topics above should not exceed 250 words and should describe the study methods results and conclusions They should be submitted no later than December 1 1979 to
Center for Disease Control
Attention Symposium Director
International Symposium on Pelvic Inflammatory Disease
Building 1 Room 3070
Atlanta Georgia 30333

Financial assistance may be available for individuals whose abstracts are accepted

Proceedings of the Symposium will be published in a referred scientific journal

Attendance Those interested in attending the meeting should notify the Symposium Director (above address) by February 1 1980 since seating and accommodations are limited

International symposium on uterine and placental blood flow will take place at the University of Chicago Center for Continuing Eduction Chicago Illinois March 24-25 1980 Sponsored by Chicago Heart Association and the University of Chicago Department of Obstetrics and Gynecology Supported by the National Institutes of Health

The program will include speakers from various disciplines of medicine Discussion will stress methodology physiological and pharmacological influences on blood flow and various stress factors Speakers will be investigators in the field of vascular smooth muscle in general and uterine and placental blood flow in particular The program is intended to summarize recent research and critically review the subject Attendance is limited to 100 on a first-come first serve basis

Category I AMA Physician Recognition Award credit hours and Cognates from the American College of Obstetricians and Gynecologists have been applied for

For further information contact
Susan A Sh kelle
Section Head
Preventive Cardiology
Chicago Heart Association
20 North Wacker Drive
Chicago Illinois 60606
USA

Acta Obstet Gynecol Scand 58 453–455 1979

INTRAMUSCULAR ACTH OR PLACEBO IN THE TREATMENT OF HYPEREMESIS GRAVIDARUM

Olavi Ylikorkala Antti Kauppila and Maija Liisa Ollanketo

From the Department of Obstetrics and Gynecology University of Oulu Oulu Finland

Abstract Thirty two women with hyperemesis gravidarum were treated with intramuscular ACTH (0 5 mg) or placebo for 4 days in a randomized double blind trial The two treatments were equally effective in relieving hyperemesis although the function of the adrenal cortex was stimulated only during the ACTH therapy The administration of ACTH thus appears useless for the treatment of severe vomiting in early pregnancy

The specific etiology of hyperemesis gravidarum is still unknown Hypofunction of the anterior pituitary and of the adrenal cortex has often been assumed to play a role in its development (6 9) Consequently hyperemesis has been successfully treated with ACTH (1 3 7) but unfortunately these studies were not placebo controlled

Recent studies showed no hypofunction of the pituitary adrenal axis in hyperemesis (8 10) On the contrary the circulating levels of ACTH and cortisol were higher in hyperemesis than in normal early pregnancy (8) These observatons lend no rational support to the administration of ACTH which is however still used for the treatment of hyperemesis Therefore we did a double blind placebo controlled study of the effectiveness of ACTH in relieving severe vomiting during early pregnancy

PATIENTS AND METHODS

In 32 patients admitted to hospital because of hyperemesis gravidarum the vomiting did not stop or decrease significantly during the first 2 days in hospital (Table I) These patients were included in this trial and given 0 5 mg of synthetic ACTH (tetracosactid) or placebo intramuscularly in a randomized order on 4 consecutive days The ampules were numbered and similar in appearance (by courtesy of Organon Oss The Netherlands) The patients were observed in the ward for 6 more days after the initial injection Intravenous fluid and electrolytes were administered at any time during the hospitalization when they were considered to be medically indicated No other treatment was used

A special questionnaire was designed for recording the symptoms before the admission during the hospitalization and after discharge In addition the nurses counted the daily number of vomiting attacks and weighed the patients every second day A scoring system was developed for an assessment of the severity of hyperemesis before the hospitalization and for the determinationof the therapeutic effect of the treatment (Table II)

Before the start of the trial a blood sample was taken at 8 a m and at 4 p m for the measurement of cortisol (5) and the 24-hour urine was collected for the assay of 17 keto-steroids and 17 ketogenic steroids (2) These tests were repeated on the 4th 6th and 8th day Student s t test was employed for evaluating the differences

RESULTS

The groups were comparable with respect to the patients age parity and gestational age as well as to the severity of hyperemesis (Table I Fig 1) The severity score was 9 7±2 2 (mean±SD) in the ACTH group and 11 1±3 3 in the placebo group ($p>0\ 05$) (Fig 1)

In all patients the vomiting disappeared during the hospitalization but no sooner in women treated with ACTH than in those treated with placebo (Table III) The ACTH than in those treated with placebo (Table III) The ACTH group showed a slightly higher weight gain than the placebo group but the difference

Table I *Clinical data on 32 patients with hyperemesis gravidarum*

	ACTH	Placebo
Number of patients	16	16
Age (years) (mean±SD)	25 3±2 8	25 8±4 3
Parity		
Nulliparous	8	6
I parous	7	6
II parous	1	4
Gestational age (weeks)	10 3±2 8	10 6±2 8

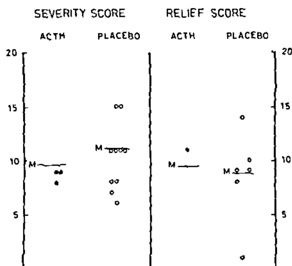


Fig 1 Individual severity and relief scores in the ACTH and placebo groups groups (see Table II) The horizontal lines indicate the mean scores

was not statistically significant The number of readmissions and the outcome of pregnancy were similar in the two groups The therapeutic response measured with the scoring system did not display any difference between ACTH and placebo (Fig 1) The mean relief score was 9 4±3 4 in the ACTH group and 8 8±3 1 in the placebo group ($p>0\ 05$)

The levels of cortisol displayed a normal circadian ion and were similar in the two groups before eatment as were the urinary excretions of etosteroids and 17 ketogenic steroids (Fig 2 and

The administration of ACTH caused a significant increase ($p<0\ 001$) in blood cortisol which returned to the pretreatment level 2 days after the last ACTH injection (Fig 2) A similar response was seen in the urinary excretion of 17 ketosteroids and 17 ketogenic steroids (Fig 3)

DISCUSSION

ACTH has been used for the treatment of hyperemesis gravidarum for more than 20 years It stopped the vomiting in all patients studied when given intravenously or intramuscularly (1 3 7) However such studies are hampered by the lack of placebo controls and any kind of treatment can be curative in a syndrome such as hyperemesis where emotional factors may be of great importance in the etiology (4)

In the present double blind study the dose of ACTH was big enough to stimulate the function of the adrenal cortex The slightly higher weight gain in the ACTH group may be due to this stimulation and a consequent fluid retention ACTH however did not exert any specific therapeutic effect on vomiting This agrees with previous results showing that there is no hypofunction of the pituitary adrenal axis in hyperemesis (8 10) Therefore ACTH should not be used any more for the treatment of hyperemesis

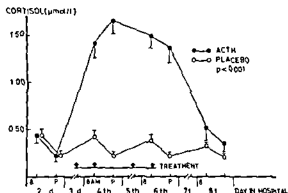


Fig 2 Circulating cortisol (µmol/l) (mean±SEM) in patients treated with ACTH or placebo

REFERENCES

1 Carreras B B Intravenous ACTH in the treatment of hyperemesis gravidarum Obstet Gynecol *3* 50 19 4
2 Eglof M Degrelle H & Jayle M F *Dosag semi automatique en flux continu des 17 cetosteroides urinaires* Clin Chim Acta *59* 147 1975
3 Erb von H & Keller M ACTH Behandlung bei schwerem Schwangerschafts erbrechen Gynaecologia *152* 258 1961

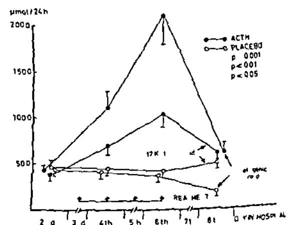


Fig 3 Urinary excretion (µmol/24 hours) (me n±SEM) of 17 ketosteroids and 17 ketogenic steroids in patients trea ed with ACTH or placebo

Table II *The scoring system for the assessment of the severity of hyperemesis before treatment and for the evaluation of the therapeutic effect of the treatment The most severe hyperemesis can cause 20 and the most effective treatment 15 scores*

Severity scores	Score	Relief* score	Score
Duration of vomiting		**Weight change (kg)**	
less than 5 days	1	decreased	−4
6−7 days	2	no change	−2
more than one week	3	increased 0−1	1
No of vomiting attacks daily		increased 1.1−2.0	2
4 or less	1	increased 2.1−3.0	3
5−7	2	3.1 or more	4
8−9	5	**Vomiting**	
10 or more	7	became worse	−3
Weight decrease (kg)		no change	0
less than 2	2	relieved	2
2−4	4	disappeared	3
5 or more	6	**Acetonuria**	
Acetonuria		did not disappear at all or later than the 5th day	−2
positive (+)	1	disappeared on the 5th day	1
strongly positive (++)	2	disappeared on the 4th day	2
Dehydration on admission		disappeared on the 3rd day	3
hematocrit less than 39	1	**Readmission to hospital**	
hematocrit more than 39	2	yes	−4
		no	2
		Patient's opinion about treatment	
		no relief	0
		little relief	1
		relieved well	2
		relieved very well	3

* M lost Ames Gothenburg Sweden

4 Fairwheather D A I Nausea and vomiting in pregnancy Am J Obstet Gynecol *102* 135 1968
5 Fiorelli G Piolanti P Forti G & Serio M Determination of plasma corticosteroids and urinary cortisol by competetive protein binding method using dextran coated charcoal Clin Chim Acta *37* 179 1972
6 Järvinen P A & Uuspää V J The response of the adrenal cortex to ACTH in hyperemesis gravidarum Acta Endocrinol *17* 211 1954
7 Järvinen P A & Uuspää V J Treatment of hyperemesis gravidarum with ACTH Ann Chir Gynecol Fenn *44* 170 1955
8 Kauppila A Ylikorkala O Järvinen P A & Haapalahti J The function of the anterior pituitary adrenal cortex axis in hyperemesis gravidarum Br J Obstet Gynecol *83* 11 1976
9 Kemp W N The treatment of early vomiting of pregnancy with suprarenal cortex Case reports Endocrinology *16* 434 1932
10 Ylikorkala O Kauppila A & Haapalahti J Follicle stimulating hormone thyrotrophin human growth hormone and prolactin in hyperemesis gravidarum Br J Obstet Gynecol *83* 528 1976

Table III *Clinical outcome*

	ACTH	Placebo
Vomiting stopped during hospitalization	16/16	16/16
Interval between admission and cessation of vomiting (days)	5.1±2.4	4.9±1.9
Weight gain in the ward (kg)	2.5±0.9	1.5±1.0
Readmission	2	2
Spontaneous abortion	1	1
Premature labor	1	0
Birth weight (g)	3 [illegible]13±379	3 506±497
Not yet delivered	3	4

(36th week)

Submitted for publication June 6 19[illegible]8

Olavi Ylikorkala M D
Department of Obstetrics and Gynecology
University of Oulu
SF 90220 Oulu 22
Finland

ANNOUNCEMENT

The 22nd British Congress of Obstetrics and Gynaecology will be held in Edinburgh from 8th 11th July 1980
For further information apply to
Congress Office
Royal College of Obstetricians & Gynaecologists
27 Sussex Place
Regent s Park
London NW1 4RG
England

The Twenty first Postgraduate Institute for Pathologists in Clinical Cytopathology is to be given at The Johns Hopkins *University School of Medicine and The Johns Hopkins* Hospital Baltimore Maryland April 14 25 1980

The full two week program is designed for Pathologists who are Certified (or qualified) by the American Board of Pathology (PA) or their international equivalents

Information
John K Frost M D
610 Pathology Building
The Johns Hopkins Hospital
Baltimore Maryland 21205
USA

Application is to be made before March 7 1980

Official language English

Acta Obstet Gynecol Scand 58 457–460 1979

PREDICTION OF THE TIME OF DELIVERY BY MEANS OF ULTRASONIC SCANNING BETWEEN THE 20TH AND 30TH WEEKS OF PREGNANCY

Ernst Hasch Aksel P Lange and Torsten Sørensen

From the Department of Obstetrics and Gynecology Kolding Hospital Kolding Denmark

Abstract Ultrasonic scanning with measurement of the biparietal diameter during the 20th and 30th weeks of pregnancy has been carried out on 738 women with an uncomplicated pregnancy and spontaneous delivery of a healthy child weighing more than 2 500 g The time of delivery was thereafter calculated by means of a reference curve

A total of 642 women had a reliable calculated expected date of delivery using information regarding the last menstrual period and clinical examination but in 96 women this was considered as unknown or uncertain

The cumulative curve of the time of delivery determined by ultrasonic scanning in relation to the actual time of delivery was similar for the two groups as an expression of a reliable and independent measuring technique Division into early and late timing of measurement showed no definite difference in the prediction

In the group of women with reliable dates it was found that the calculated expected delivery date using biparietal diameter measurement lay on average 5-6 days later This can be explained by the difference in sound speed between the apparatus used to determine the reference curve and that employed for the present investigation

In the group with a reliable expected date of delivery 92 per cent gave birth within ±14 days of term as calculated from menstrual data and 87 per cent within ±14 days of term as calculated from the biparietal diameter

In the group with uncertain dates 83 per cent gave birth within ±14 days in relation to the time of delivery alculated from ultrasonic scanning

It is concluded that it is possible with an acceptable margin of safety to predict the time of delivery of a patient on the basis of a single measurement of the biparietal diameter between the 20th and 30th weeks of pregnancy

A measurement of the biparietal diameter at this time is of additional importance as the basal value should the pregnancy be complicated later by the need for regular measurement of the biparietal diameter

Ultrasonic scanning has gradually become of more importance in later years within the field of obstetrics as this non invasive method of examination gives reliable information on various fetal measurements the fetal position the number of fetuses as well as the site of the placenta

This method has been used since first described by Campbell (1) for the measurement of the biparietal diameter (BPD) in an attempt to determine fetal maturity the time of delivery and by serial measurements to demonstrate a reduction in or lack of growth of the fetus (2 3 4 6 7 8 10)

Ultrasonic scanning has been used since 1972 in our department as a routine examination between the 20th and 30th weeks of pregnancy in all pregnant women

The object of the present investigation has been to evaluate the accuracy of BPD measurement carried out at this period of pregnancy in predicting the time of delivery

EXAMINATION METHOD

The scanning of pregnant women was carried out in the ultrasonic laboratory by nurses without special obstetric training but with special training in ultrasonic scanning

The bistabil technique was used during the first years but replaced by the grey tone technique later A sound frequency of 2 25 mHz and a sound speed of 1 560 m/sec is employed The duration of the examination is 10-15 minutes

The BPD in this study was measured in contrast to newer measuring methods using electronic marking on polaroid photographs of the A presentation (i e projection of the echoes as spikes along a graduated base line on an oscilloscope) after a scanning section had been produced of the head of the fetus with a clear midline structure (Fig 1) The BPD estimated time of delivery (BPD term) was thereafter determined by comparing the measurements with a growth table of BPD as published by Levi *et al* (7)

The time of delivery was also calculated from information regarding the last menstrual period (LM term) in those cases where this was reliable and where it was in agreement with the first clinical examination

The difference between the calculated and actual time of delivery was thereafter determined and recorded

PATIENTS AND RESULTS

One thousand consecutive patients were included in the investigation which was retrospective Their case histories were studied and 738 patients selected as their pregnancy was normal or had only slight complications which were presumed to have had no influence on the duration of pregnancy





pper Longitudinal scanning section of a 24 weeks s Head with midline to the right trunk to the left ymphysis U Umbilicus
Middle Transvers section of *the same* patient in the *um* bilical plane demonstrating fetal head with midline echo
Below The A presentation with near and far skull echoes *together* with midline echoes *BPD measurement* indicated

Birth occurred spontaneously with the delivery of a healthy child weighing more than 2 500 g

The 738 patients were divided into two groups

Group I consisting of 642 women with a reliably determined *time of* delivery i e definite information regarding the last menstrual period regular menstrual cycle with a length not exceeding 35 days and no *disagreement* between the size of the uterus and the calculated time of delivery at the first clinical examination

Group II consisting of 96 patients whose time of delivery was considered as either unknown or uncertain either owing to lack of information or uncertainty *regarding the* last menstural period or disagreement between a definite last menstrual period and the first clinical examination

The distribution according to the timing of the measurement for the patients in group I is shown in Fig 2

The cumulative curves for the calculated time of delivery using *the BPD measurement* for these two groups in relation to the actual time of delivery are shown in Fig 3 From these it can be seen that the curves are practically the same (P 0 8 0 9 x^2-test)

In group I 87 per cent of the patients were delivered within ±14 days of the BPD term The same figure for group II was 83 per cent of the patients

A division of the patients *in group I into early* and late time of scanning gave no definite difference in the prediction of the time of delivery

The relationship between the BPD term and the LM term in group I where there was a reliable expected date of delivery is shown in Fig 4 This shows that the cumulative curves for the BPD term and the LM term re pectively *in relation to* the actual time of delivery have an almost parallel course but clearly show that the BPD term lies on average 5 6 days later than the LM term in the range 15 days prior to and 20 days after delivery

The difference between the BPD term and *LM* term was less than 14 days in 94 5 per cent of the cases

While delivery as mentioned earlier occurred within ±14 days of the BPD term in 87 per cent of the patients in group I the corresponding percentage according to the LM term was 92

DISCUSSION

This investigation has shown that ultrasonic scanning with measurement of the biparietal diameter of the fetus between the 20th and 30th weeks of pregnancy provides a reasonably *sound* basis for the calculation of the patient s time *of delivery* and one that compares well with term as calculated *from* reliable information *regarding* the last *menstrual* period

The fact that the cumulative curves of *the* calculated BPD term for patients with known *unknown* or uncertain time of delivery *using information* based on the *last menstrual* period *almost* lie on top of each other shows that the measuring *method* is independent of eventual knowledge by the *patient* of the predicted time of delivery

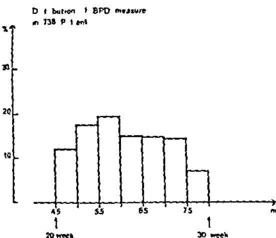


Fig 2 Distribution of BPD measurements in the 738 patients included in the study

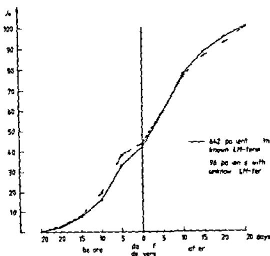


Fig 4 Cumulative curves of BPD-term (—) and LM term (—) in relation to date of spontaneous delivery in 647 patients

A comparison between the predicted term according to the last menstrual period in a group of patients where this information was reliable with the BPD term showed that the latter lay on average 5-6 days later The explanation of this discrepancy must presumably by sought in the fact that the reference curve was compiled using an apparatus with a sound speed of 1 529 m/sec while the apparatus employed in the present investigation has a sound speed of 1 560 m/sec This difference of 2 per cent will with a pregnancy of 280 days give just this difference of 5-6 days It is thus important that the individual laboratories ensure that the sound speed used in the compiling of the reference curve and that of the equipment in the laboratory are similar or at least that a correction is made in the reference curve for this difference

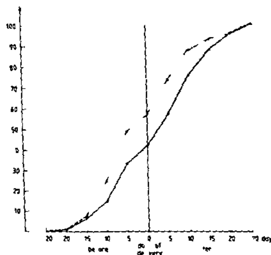


Fig 3 Cumulative curves of BPD-term in relation to date of spontaneous delivery in 64 patients with known LM term (—) and 96 patients with unknown LM term (—)

Our results show that a BPD measurment carried out between the 20th and 30th weeks of pregnancy in cases where the expected time delivery is unknown or uncertain will be of almost the same value as if the patient had been certain of the date of the last menstrual period Ultrasonic scanning may be considered as superior to other methods for e g the time of observing the first signs of life clinical or X ray examination

Using the same method as employed in the present study Campbell (2) found that 84 per cent of patients gave birth within ±9 days Underhill *et al* (10) found that 80 per cent gave birth within ±14 days Varma (11) obtained even more impressive results with 91 per cent delivering within ±9 days patients with signs of intrauterine growth retardation having been excluded from her investigation

We consider our results as acceptable in comparison with those of others particularly as the investigation was carried out by staff not versed in obstetric practise

Within the last couple of years a new fetal measure has been employed for the prediction of the time of delivery namely the crown rump-length carried out between th 7th and 14th weeks of pregnancy (9)

Using this measurement Drumm (5) showed that 96 per cent of the cases delivered within ±12 days of the predicted time in other words a considerable im provement in the results obtained by employing the BPD measurement

However this method is hardly suitable for routine use owing to the fact that it is carried out very early in pregnancy at a time when the patient has not com menced attending for prenatal assessment

We consider on the basis of our results that we can recommend the routine measurement of BPD be tween the 20th and 30th weeks of pregnancy on as many pregnant women as possible along with the other screening procedures to which pregnant women are subjected

We also recommend that only a limited number of *staff carry out the BPD measurement so that they* may obtain as much experience as possible thus enhancing the accuracy and therefore the value of BPD measurement

REFERENCES

1 Campbell S An improved method of fetal cephalometry by ultrasound J Obstet Gynaec Brit Comm *75* 568 1968

2 Campbell S The prediction of fetal maturity by ultrasonic measurement of the biparietal diameter J Obstet Gynaec Brit Comm *76* 603 1969

ll S & Dewhurst C J Diagnosis of the small dates fetus by serial ultrasonic cephalometry Lancet 1002 1971

4 Campbell S The assessment of fetal development by diagnostic ultrasound Clinics in Perinatology *1* 507 1974

5 Drumm J E The prediction of delivery dates by ultrasonic measurement of fetal crown rump length Brit J Obstet Gynaec *84* 1 1977

6 Flamme P Ultrasound fetal cephalometry percentiles curve Brit Med J *3* 384 1972

7 Levi S & Smets P Intra uterine fetal growth studied by ultrasonic biparietal measurements Acta Obstet Gynecol Scand *52* 193 1973

8 Jouppila P Ylöstalo P & Pystynen P Fetal head growth measured by ultrasound in the last few weeks of pregnancy in normal toxaemic and diabetic women Acta Obstet Gynecol Scand *49* 367 1970

9 Robinson H P Sonar measurement of fetal crown rump length as a means of assessing maturity in the first trimester of pregnancy Brit Med J *4* 28 1973

10 Underhill R A Beazley J M & Campbell S Com parison of ultrasound cephalometry radiology and li qour studies in patients with unknown confinement dates Brit Med J *3* 736 1971

11 Varma Th R Prediction of delivery date by ultra sound cephalometry J Obstet Gynaec Brit Comm *80* 316 1973

Submitted for publication July 27 1978

Ernst Hasch M D
Department of Obstetrics and Gynecology
Kolding Hospital
DK 6000 Kolding
Denmark

Acta Obstet Gynecol Scand 58 461 – 467 1979

VAGINAL BLEEDING IN THE LAST TWO TRIMESTERS OF PREGNANCY
A CLINICAL AND ULTRASONIC STUDY

Pentti Jouppila

From the Department of Obstetrics and Gynecology University of Oulu Oulu Finland

Abstract Ninety seven cases of vaginal bleeding during the second and third trimesters of pregnancy are presented with special reference to the follow up observations and perinatal parameters after the first bleeding and ultrasonic determination of placental site The perinatal mortality rate was 11 per cent and the rate of premature deliveries 23 per cent In the cases of recurrent bleeding episodes (N=33) the corresponding frequencies were 22 and 35 per cent Placenta previa of some degree was diagnosed by ultrasound during the first episode of bleeding in 36 cases Although the placenta was observed to move upwards from the internal os of cervix in 20 of these patients during the last few weeks of pregnancy final placenta previa (N=16) was the most common definite etiological factor behind the bleeding The high frequency of perinatal complications associated with these pregnancies emphasizes despite reliable localization of the placenta the importance of a careful follow up until delivery

Bleeding during the last few months of pregnancy generally requires an etiological clarification of the possible causes in hospital Even after careful application of modern diagnostic tools however the etiology seems to remain unclear in 38 per cent of the cases (10) or the origin of bleeding is obviously some extrinsic factor (polyps bleeding of incompetent cervix etc) The role of placenta previa is nevertheless very important its frequency in the cases with bleeding during the second half of pregnancy being 12 25 per cent (2 7 10) and during the last trimester as high as 75 per cent (1) Premature separation of the placenta is the most dangerous cause of bleeding for the fetus and the perinatal mortality as a consequence of this situation is up to 83 per cent (10) The prognosis for the fetus seems universally to become more grave with an increasing amount of bleeding an increasing number of bleeding episodes and an early onset of the bleeding (8 9 10)

With the introduction of diagnostic ultrasound during the last ten years the accuracy with which the placenta can be localized has markedly improved The most important objective in the ultrasonic diagnosis of bleeding patients is to clarify th anatomical relation between the internal os of the cer vix and the caudal end of the placenta It is also ver important to bear in mind that the placenta frequent ly moves due to the formation of the isthmic seg ment of the uterus from the internal os to the fundu during the last 5 10 weeks of pregnancy which mear that early diagnosis of placenta previa must be cor firmed by later ultrasonic examinations (4 6)

The purpose of this work was to examine th clinical findings and the outcome of the pregnancy i cases of patients hospitalized for diagnosis of vagin: bleeding during the last two trimesters of pregnancy Special attention was paid to the ultrasonic localiza tion of the placenta and to the follow up of th placental site during the subsequent course of th pregnancy

MATERIAL AND METHODS

The series consists of 97 patients hospitalized for vaginal bleeding in the 14th-40th weeks of pregnancy during the years 1975 1977 All cases requiring emergency intervention in the early stage of bleeding and those in which the bleeding was connected with the initiation of delivery were excluded 29 of the patients were primigravid The bleeding began in the 14th 27th gestational week in 64 and in the 28th-40th week in 33 patients The duration of the first episode of bleeding was 1 2 days in 66 3-4 days in 15 and 5 days or more in 16 cases Fetal life signs were detected by ultrasound in all cases and hence there were no cases with missed abortion or blighted ova

The ultrasonic localization of the placenta was performed during the first days after admission using the full bladder technique (Kretz Combison equipped with a grey scale for the last year) The cases of placenta previa were subclassified as marginal partial and total placentas with low insertion were not included in this classification If placenta previa of some degree was detected at the first examination (36 patients) follow up examinations were made at 2 week intervals until the final diagnosis of the site of placenta Hence the number of ultrasonic examinations totaled 188

A vaginal examination was performed on all the patients in order to diagnose the possible extrinsic cause of the

Table I *Perinatal parameteres of the material (N=97)*

Perinatal mortality		Premature deliveries (< 37th week)		Congenital anomalies	
No	per cent	No	per cent	No	per cent
10	11	21	23	5	6

In the calculations of percentage frequencies are the late abortions excluded from the total material

bleeding and a vaginal and cervical smear for the Papanicolaou examination was also taken All the cases were followed until the end of pregnancy The number of bleeding episodes the week of delivery the perinatal mortality rate and the congenital anomalies of the newborn infants were observed The most probable cause of the bleeding was sought taking into consideration the clinical and ultrasonic findings during the bleeding episodes and the observations during and after delivery

The statistical analyses were made with Student s t test

RESULTS

The perinatal data for the series are presented in Table I The perinatal mortality was 11 per cent and the frequency of premature deliveries 23 per cent The number of late abortions in this material was seven

Onset of bleeding The occurrence of the first ing episode in the second (N=64) rather than u trimester (N=33) of pregnancy had no effect on the rate of perinatal mortality or final frequency of placenta previa Repeated bleeding episodes and premature deliveries were however almost significantly ($p<0\ 05$) more common in the group where bleeding started in the second trimeste

Duration of the first bleeding For cases where the first bleeding episode continued for 5 days or more the perinatal mortality was 35 per cent This mortality was highly significantly ($p<0\ 001$) more frequent than in the group with a shorter bleeding episode The other differences between these groups were non significant

Repeated bleeding episodes The vaginal bleeding was observed to recur during the subsequent course of the pregnancy in 33 cases In this group the perinatal mortality rate (22 per cent) and the frequency of premature deliveries (35 per cent) were significantly ($p<0\ 01$) higher compared with the other patients

Placental site At the first examination immediately after the first bleeding placenta previa of some degree was diagnosed by ultrasound in 36 cases Of these patients 26 had the onset of bleeding during the second trimester and 10 during the third Recurrent bleeding episodes were observed in 54 per cent of this previa group a frequency that differed significantly ($p<0\ 01$) from the patients with an upper location of the placenta

The final diagnosis of placenta previa was made in connection with delivery in 16 cases (total previa in five partial in four and marginal in seven) Migration of the placenta from the area of the internal os was observed in the consecutive ultrasonic examinations of 20 patients (Fig 1 2 3 and 4) An example of a non moving total placenta previa is presented in Fig 5 and 6 The mode of delivery in cases with final placenta previa was cesarean section in 14 and vaginal in two The frequency of prematurity (37%) in the final placenta previa group was almost significantly ($p<0\ 05$) higher than in the group with normal location of the placenta However the PNM rate (N=3) did not differ between these groups All the patients except one were multigravid In three cases of placenta previa partial premature separation of the placenta was observed upon delivery The first bleeding occurred as often during the second as during the third trimester of pregnancy

The last ultrasonic examination 1 14 days before delivery gave the exact diagnosis of the degree of placenta previa in 11 cases In two cases where the last ultrasonic diagnosis was partial placenta previa

Table II *Placental site according to the last ultrasonic examination*

	No	per cent
Anterior	27	28
Posterior	35	36
Fundal	10	10
Right lateral	5	5
Left lateral	4	4
Posterior previa	10	10
Anterior previa	6	6

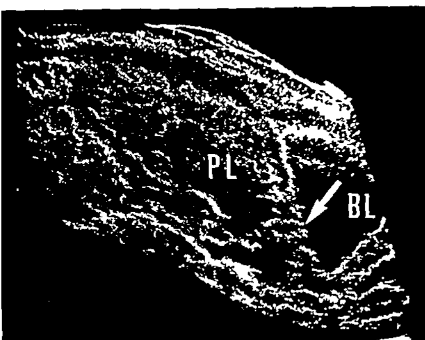


Fig 1 Longitudinal ultrasonic B scan at the 27th week of pregnancy Total placenta previa (PL) on the anterior wall of the uterus
BL = urinary bladder arrow indicates the area of internal os of cervix

marginal previa was observed during the first stage of labor In both cases the placenta was located on the posterior wall In three patients undergoing cesarean section the placental site was total previa contrary to the ultrasonic diagnosis of partial placenta previa

The placental locations according to the last ultrasonic examination are presented in Table II Posterior placentas seem to be more frequent than anterior

Most probable etiology of the bleeding By combining the observations made during the bleeding episodes and upon delivery an attempt was made to postulate the main etiological cause of the bleeding

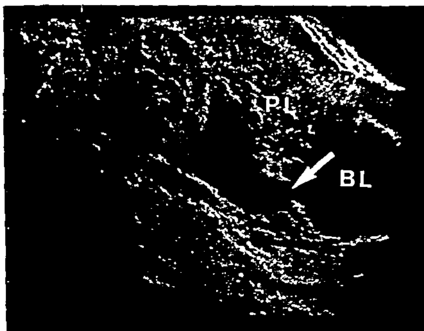


Fig 2 Ultrasonic B scan at the 31st week from the same patient as in Fig 1 Marginal placenta previa

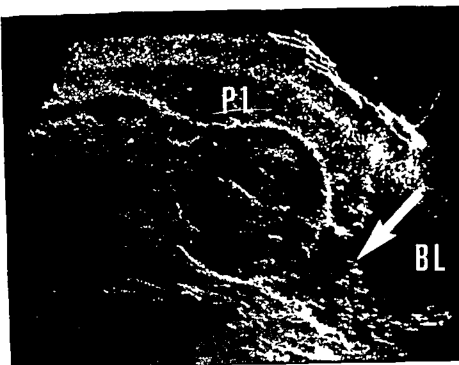


Fig 3 Ultrasonic B scan at the 33rd week from the same patient as in Fig 1 and 2 The degree of placenta previa is further marginal

(Table III) In 23 cases it proved impossible to establish a background to the bleeding In 20 patients the placental site was previa of some degree during the first bleeding episode without any other etiology for the bleeding but during the subsequent course of pregnancy the placentas moved to the upper parts of the uterus thereby leaving the final etiology of the bleeding slightly obscure The frequencies of cervical erosions (11 per cent) polyps (6 per cent) and incompetent cervix (6 per cent) were relatively high but that of a rupture of sinus marginalis was only 4 per cent There were no cases with just premature separation of the placenta



Fig 4 Ultrasonic B scan at the 39th week from the same patient as in Fig 1 2 and 3 Placenta on the anterior wall of the uterus away from the area of internal os of cervix



Fig 5 Longitudinal ultrasonic B-scan demonstrating total placenta previa on the posterior wall of the uterus at the 23rd week of pregnancy

DISCUSSION

According to the results of this study bleeding during the second or third trimester of pregnancy carries a perinatal mortality of 11 per cent and a 23 per cent frequency of premature deliveries These frequencies differ highly significantly ($p<0.001$) from the corresponding rates (1 5 per cent and 5 2 per cent) recorded at the Department of Obstetrics and Gynecology University of Oulu during the same years 1975 77 Hence these patients must be classified into a high risk group from the first onset of bleeding until the end of the pregnancy

In an earlier study from the same clinic it was observed that after bleeding during he first trimester

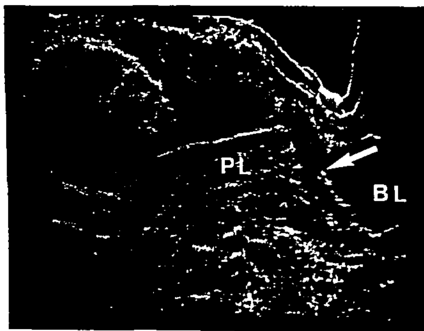


Fig 6 Ultrasonic B scan at the 37th week from the same patient as in Fig 5 Placenta is still in the same previous location on the posterior wall of the uterus

Table III *The most probable etiological factor of bleeding*

	No	per cent
Undetermined cause	23	24
Placenta previa during the first bleeding not indicating at delivery	20	21
Placenta previa at delivery	16	17
Cervical erosion	11	11
Cervical polyp	6	6
Cervical imcompetence	6	6
Late abortion	7	7
Rupture of sinus marginalis	3	3
Others (dysplasia cervicis kolpitis etc)	5	5

of pregnancy (3) the frequency of premature deliveries was also rather high (13 2 per cent) if the fetus was alive at the time of the symptoms of threatened abortion The frequency of placenta previa at delivery was low (3 per cent) which agrees with other follow up examinations after threatened abortion (5 11) The perinatal mortality rates were also relatively close to the normal frequencies It therefore seems that bleeding during the last two trimesters of pregnancy signifies a markedly higher risk for full term continuation of pregnancy and for perinatal parameters

A long duration of the first bleeding episode and ally a recurrence of bleeding episodes seemed augment the effect on perinatal mortality which rees with the earlier observations (10) It is obvious that placenta previa of some degree is a very common cause of recurrent bleedings for in the present examination this location of the placenta was observed in 54 per cent during the first episode of bleeding

The tendency for placental migration away from the cervical area during the last trimester of pregnancy observed in this study agrees with the earlier reports (4 6) Though the placentas with low insertion were not included in the previa group the frequency of definite placenta previas was 17 per cent and this was the most common etiological cause of the bleeding In addition to this group 20 patients had placenta previa during the first bleeding episode but a normal placental location during the last few weeks of pregnancy Thus examination of the placental site combined with a clinical examination is the most important diagnostic tool for bleeding patients If the placenta is in a previous location during the bleeding episode the placental site must be examined by ultrasound until migration is observed or a final diagnosis of placenta previa without an upward moving tendency can be made For this follow up period it is best to keep the patient in hospital In this series the recurrent bleeding was often heavy and the fetus could only be saved with an emergency cesarean section Half of the final placenta previa patients had the first bleeding before the end of the second trimester which contradicts a common opinion (1)

The placentas in this series were more often on the posterior than the anterior wall of the uterus which disagrees with the results of Kurjak (1977) but explains some difficulties in the exact determination of the degree of placenta previa Even with the fullbladder technique the overshadowing effect of the fetal parts on the ultrasonic examination occasionally disturbs the location of the lower part of the posterior placenta in relation to the internal cervical os

In conclusion it can be stated that bleeding after the first trimester of pregnancy leads to a high frequency of premature deliveries and a high perinatal mortality rate Ultrasonic localization and follow up of the placenta in relation to the cervix are the primary diagnostic methods for these patients

REFERENCES

1 Brody S *In* Obstetrik och gynekologi p 233 and 237 Almqvist & Wiksell Stockholm 1970
2 Hibbard B M Simplified placental localization Br Med J 3 85 1969
3 Jouppila P & Koivisto M The prognosis of pregnancy after threatened abortion Ann Chir Gynaecol Fenn *63* 439 1974
4 King D L Placental migration demonstrated by ultrasonography Radiology *109* 163 1973
5 Kohorn E I Morrison J & Ashford C Ultrasonic scanning in obstetrics and gynecology Obs et Gynecol *34* 515 1969
6 Kurjak A & Barsic B Changes of placental site diagnosed by repeated ultrasonic examination Acta Obstet Gynecol Scand *56* 161 1977
7 Meyenburg H Über die Lokalisation der Placenta mittels Ultraschall und ihre Bedeutung für die geburtshilfliche Diagnostik Zentralbl Gynäk *95* 1400 1973
8 Peckham C H Uterine bleeding during pregnancy I When not followed by immediately termination of pregnancy Obstet Gynecol *35* 937 1970
9 Pedowitz P Placenta previa *An evaluation of expectant management and the factors responsible for fetal wastage* Am J Obstet Gynecol *93* 16 1965

10 Scott J R Vaginal bleeding in the midtrimester of pregnancy Am J Obstet Gynecol *113* 329 1972
11 Smith C Gregori C A & Breen J L Ultrasonography in threatened abortion Obstet Gynecol *51* 173 1978

Submitted for publication June 15 1978

Pentti Jouppila M D
Department of Obstetrics and Gynecology
University of Oulu
SF 90220 Oulu 22
Finland

Acta Obstet Gynecol Scand 58 469 – 472 1979

PUERPERAL LACTATION SUPPRESSION AND PROLACTIN

Herman De Gezelle Marc Dhont Michel Thiery and Walter Parewyck

From the Departments of Obstetrics and Gynecology University of Gent Gent Belgium

Abstract Five methods for puerperal lactation inhibition were assessed in a randomized fashion The 90 women were divided into five groups Four of these received a pharmacologic treatment oral stilbestrol (15 mg dd for 5 days) a diuretic compound (bendroflumethazide 15 mg dd for 5 days) by mouth oral bromocriptine (5 mg dd for 14 days) or an intramuscular injection containing estradiol (10 mg and testosterone (200 mg) esters administered immediately after delivery To the women in the remaining group only physical methods were applied (breast support and local infra red waves) and they served as controls

Prolactin plasma concentrations were determined daily for five consecutive days and showed a correlation with the clinical effectiveness of the various treatment schedules While bromocriptine reduced and stilbestrol augmented prolactin levels both types of treatment were equally effective in preventing lactation during the observation period Treatment with a diuretic compound or with an injection of steroids though less effective than the first two regimens was nevertheless significantly more efficacious than physical treatment

During the last few decades a whole array of methods has been proposed for the suppression of puerperal lactation ranging from ice bags and tight breast binders to hormonal regimens The method currently applied in our department consists in a single intramuscular injection of estradiol and testosterone esters administered immediately after the delivery and supplemented by oral diuretics when the mother complains of breast tenderness or milk secretion

Recent findings in lactation physiology and the ability to determine human prolactin (hPRL) in blood have paved the way not only to a more rational approach but also to a reassessment of time honored methods

The purpose of this study was to assess five treatment regimens and to correlate the clinical effectiveness of each method and the effect on the hPRL plasma concentration

MATERIAL AND METHODS

Ninety clinically normal women who had gone through a normal term delivery and who chose not to breastfeed were studied The purpose of the study was explained to them and their consent was obtained

Treatment regimens were randomly assigned to five groups of 18 women each and each group had equal numbers of primi and multiparae

1 *The control group* received no specific medication but the women were advised to wear a well fitting brassiere night and day and infra red lamp was applied to the breasts three times daily for ten minutes each time

2 *Women in the stilbestrol group* received 5 mg diethyl stilbestrol (Distilbène R) by mouth three times daily for five days Treatment was started within six hours of delivery

3 The members of the *diuretic group* were given 5 mg bendroflumethazide (Pluryl R) orally three times daily for five days This treatment too was started within six hours of delivery

4 *Estradiol+testosterone (E+T) group* These women were given a single dose of a mixture of estradiol esters (10 mg) and testosteron esters (00 mg) in olive oil (Estandron prolongatum R) intramuscularly immediately after delivery

5 *The bromocriptine group* recieved a daily oral dose of 5 mg bromocriptine (Parlodel R) for fourteen days starting within six hours of delivery

Complaints of breast tenderness or engorgement and milk secretion were noted every morning at 8 a m for five consecutive days by the same nurse who had no knowledge of the type of treatment applied Signs and symptoms were graded as absent mild moderate or severe A blood sample was taken from all of the patients at delivery and subsequently each morning at about 10 a m for five days The blood was allowed to coagulate and the sera were stored at 20 C until assay Prolactin concentrations were determined by a double antibody radioimmunoassay performed with the NIH kit (VLSI) All blood samples collected on the same postpartum day were run in a single assay

Differences in clinical effectiveness were analyzed statistically by the chi square test and the exact Fisher test Differences in hPRL concentrations were analyzed by two-way analysis of variance and by Student t test

RESULTS

In none of the treatment groups were significant differences found between primi and multiparae with respect to either hPRL concentration or clinical

10 Rolland R & Schellekens L A new approach to the inhibition of puerperal lactation J Obstet Gynaec Brit Cwlth *80* 915 1973
11 Schwartz J Evans C Garcia C R Rickels K & Fisher E *A clinical study of lactation suppression* Obstet Gynecol *42* 599 1973
12 Steenstrup E K & Steenstrup O R Prevention of puerperal lactation with bromocriptine (CB154) A double-blind comparison with diethylstilbestrol Current Therap Res *21* 327 1977
13 Tyson J E Huth K J & Andreassen B The influence of prolactin secretion on human lactation J Clin Endocr *40* 764 1975
14 Utian W H Begg G Vinik A J Paul M & Shuman L Effect of bromocriptine and chlorotrianisene on inhibition of lactation and serum prolactin A comparative double blind study J Obstet Gynecol *82* 755 1975
15 Varga L Lutterbeck P M Pryor J S Wenner R & Erb H Suppression of puerperal lactation with an ergot alkaloid A double blind study Brit Med J *2* 743 1972
16 Weinstein D Ben David M & Polishuk W Z Serum prolactin and the suppression of lactation Brit J Obstet Gynaec Cwlth *83* 679 1976

Submitted for publication June 6 1978

Herman De Gezelle M D
Department of Obstetrics and Gynecology
Academic Hospital
De Pintelaan
9000-Gent
Belgium

Acta Obstet Gynecol Scand 58 473 – 476 1979

ACUTE DEEP VEIN THROMBOSIS (DVT) AFTER CESAREAN SECTION

A Bergqvist D Bergqvist and T Hallböök

From the Department of Obstetrics and Gynecology and the Department of Surgery Kärnsjukhuset Skövde Sweden

Abstract In 169 consecutive women undergoing cesarean section of which 90 were performed as an emergency and 79 electively the frequency of deep vein thrombosis was evaluated with a non invasive diagnostic technique strain gauge plethysmography Three patients developed thrombosis (1 8 per cent) all after acute surgery No specific background factors were associated with the development of thrombosis In 26 of the 79 patients (33 per cent) who were plethysmographed before operation a biphasic venous emptying indicated venous outflow obstruction by the pregnant uterus

Pregnancy and certain gynecological operations are considered risk situations for the development of thromboembolic complications The risk of fatal embolism after cesarean section is sixteen times higher than after vaginal delivery (4) The true incidence of DVT after cesarean section a situation where these two risk factors are combined is not known mostly because only few studies using objective diagnostic methods have been performed This is partly due to methodological difficulties Screening with bilateral phlebography is laborious and ^{125}I fibrinogen must not be given to lactating women because of contamination of the breast milk with free ^{125}I

This screening investigation was therefore made to evaluate the frequency of DVT after cesarean section using strain gauge plethysmography a non invasive diagnostic method

MATERIAL AND METHODS

The study involved 174 consecutive patients undergoing cesarean section 90 were performed as an emergency and 84 electively For various reasons five of the 84 were plethysmographed before operation only and are excluded thus 169 are analysed Table I lists age and parity Table II shows some different background factors of possible significance for the development of DVT Table III gives operation data Ten patients having emergency operations were transfused with 70 5 units of bank blood and five of the electively operated with 6 5 units of blood

General anesthesia was induced with thiomembutal sodium (Pentothal Abbot) and maintained with suxamethonium chloride (Celocurin Vitrum) pethidine chloride (Petidin ACO) and diazepam (Valium Roche) Epidural analgesia was performed with bupivacain chloride (Marcain Bofors) and mepivacain (Carbocain Bofors) frequently supplemented with diazepam

The cesarean section was performed through a lower abdominal midline incision using a transverse lower segment section After delivery 0 2 mg of methylergotamine (Methergin Sandoz) and 5 IU of oxytocin (Syntocinon Sandoz) were injected into the myometrium The patients were mobilized after a few hours

Strain gauge plethysmography (19) with electrical calibration (10) was used as the diagnostic method Patients undergoing elective cesarean section were plethysmographed one or two days before operation and 6 7 (4 14) days after Patients undergoing acute section were plethysmographed 6 7 (5 11) days after operation

Deep vein thrombosis (DVT) was considered present when the venous emptying was less than 30 ml x min^{-1}ml^{-1} (11) The plethysmographic curves were also analysed for the presence of biphasic venous emptying as an indication of a proximal intrapelvic obstruction to the venous outflow (3 21)

RESULTS

There were three cases of postsectional DVT a frequency of 1 8 per cent In two patients the thrombosis was on the left in one bilateral All three operations were performed as an emergency the patients being aged 19 20 and 30 years None of these women were given estrogens Follow up plethysmography about two months later in one case showed progression and in two resolution of the changes One (40 years of age) developed a DVT during the pregnancy (diagnosed with phlebography thermography and plethysmography) and was treated with subcutaneous heparin from the 15th week There was no plethysmographic or thermographic evidence of progression of the thrombosis after the cesarean section She was treated prophylactically with dextran 70 during operation and every second day after One of the patiens having an emergency section showed postoperative unilateral biphasic venous emptying on plethysmography Phlebography was normal Before

Table I *Age parity and time for preoperative hospitalization in 169 women being delivered by cesarean section*

		Age (years)			Parity (no)			Time for preoperative hospitalization (days)		
	No	Mean	Median	Range	Mean	Median	Range	Mean	Median	Range
Acute section	90	28 8	28	16–43	2 1	2	1–7	4 0	1	0–50
Elective section	79	30 5	31	19–42	2 2	2	1–7	5 7	1	1–4[illegible]

section 26 patients (33 per cent) showed biphasic venous emptying (seven bilateral) The long primary venous emptying time (0 67 sec) indicates pressure from the pregnant uterus on the inferior vena cava as the cause of the biphasic emptying (3) Three patients also showed the biphasic pattern postoperatively In one this was due to a femoral hernia which also could be seen compressing the vein on phlebography In one phlebography was normal and further plethysmography three days later was also normal The later showed normal plethysmography one week after the biphasic result In both cases a reasonable interpretation is vein pressure from an intrapelvic hematoma

DISCUSSION

The real frequency of DVT after cesarean section is not known mostly because of diagnostic difficulties phlebography can hardly be used as a ng method in a large series of young women ^{125}I fibrinogen test cannot be used in pregnant lactating women because of the transport of free ^{125}I to the fetus and the milk Two recent studies used the ^{125}I fibrinogen test after cesarean section but those who wished to breastfeed their children were excluded (9 15) It has been suggested that hormonal suppression of lactation increases the frequency of DVT (7 16) we therefore wanted to study an unselected population The small number of patients in the studies by Friend and Kakkar (9) and Jackson (15) to some extent reflects the difficulty with invasive diagnostic techniques of screening Consequently we choose a non invasive method strain gauge plethysmography which is insensitive to thrombi in the calf However we were mainly interested in diagnosing proximal thrombi of a size that would influence the venous flow and result in a greater risk of pulmonary embolism Investigations with the fibrinogen test suggest that calf thrombi are rare in this group of patients

With plethysmographic screening the frequency of DVT is low and almost the same when diagnosis is based on clinical examination (Table IV) The reason for this low incidence may be the relatively young age of the patients which also makes them more mobile A comparable risk group women having elective gallbladder surgery had a similar frequency of DVT (2) On the other hand the frequency of DVT after elective gynecological operations is usually between 10 and 20 per cent (5 9 17) but these patients are on

Table II *Background factors among 169 women undergoing cesarean section*

	Acute section	Elective section
Diab tes mellitus	1	2
Earlier thrombosis	0	4
Operations		
orthopaedic	1	2
varicose veins	4	0
appendectomy	10	11
other abdominal	5	6
gynecological	3	6
cesarean section	10	27
Use of contraceptive pills	30	10
Estrogens after delivery	5	0

Table III *Some data from the operative procedure*

	Acute section	Elective section
Epidural analgesia (no)	-	23
General anesthesia (no)	88	56
Duration of operation (min)	67 3 (30–165)	87 6 (40– [illegible]10)
Blood loss during operation (ml)	517 5 (0–[illegible] 150)	603 1 (0–[illegible] 500)
Dextran during operation (no)	11	21

Table IV *The frequency of deep vein thrombosis in connection with pregnancy normal delivery and cesarean section*

	Number of patients	Frequency of thrombosis (per cent)	Diagnostic method
Pregnancy			
Hiilesmaa (12)	3 162	1 8	clinical
Aaro and Juergens (1)	32 337	0 05	clinical
Coon *et al* (6)	7 932	0 59	clinical
Normal delivery			
Hiilesmaa (12)	39 493	1 2	clinical
Daniel *et al* (7)	9 324	0 47	clinical
Husni *et al* (14)	23 485	0 08	clinical
Aaro and Juergens (1)	32 337	0 14	clinical
Friend and Kakkar (9)	117	2 6	fibrinogen test
Jackson (15)	20	0	fibrinogen test
Flessa *et al* (8)	20 000	1 2	clinical
Cesarean section			
Hiilesmaa (12)	?	2 2	clinical
Husni *et al* (14)	1 493	3	clinical
Friend and Kakkar (9)	31	0	fibrinogen test
Jackson (15)	36	0	fibrinogen test
Present series	169	1 8	plethysmography

average older than the pregnant ones Another important factor might be the immediate return to normal of fibrinolytic activity after placental removal (20 22) During operation 19 per cent of the patients received dextran 70 as a substitute for blood loss this agent is effective for thrombosis prophylaxis in gynecological patients (5) None of the patients who developed thrombosis had been given dextran during operation

As all the thrombi in this series occurred in women having emergency operations preoperative DVT cannot be strictly excluded but the plethysmographic diagnosis suggests that the thrombi were of rather recent origin

The low frequency of postsectional DVT does not indicate prophylaxis agent thrombosis The risk for development of a post thrombotic syndrome is high in patients getting a thrombus A simple non medical method of prophylaxis which has proved effective postoperatively is the use of elastic compression stockings with graded pressure (13 18) This is a possible method of prophylaxis in this type of low risk young patient

REFERENCES

1 Aaro L & Juergens J Thrombophlebitis associated with pregnancy Am J Obstet Gynecol *109* 11 8 1971
2 Bergman B Bergqvist D & Dahlgren S The incidence of venous thrombosis in the lower limbs following elective gallbladder surgery A study with the 125I fibrinogen test Uppsala J Med Sci *80* 41 1975
3 Bergqvist D & Hallböök T Biphasic venous emptying as an indication of intrapelvic venous thrombosis *In* New trends in venous diseases (ed A Kappert) p 59 Hans Huber Publ Bern Stuttgart Vienna 1977
4 Bonnar J Long term self administered heparin therapy for prevention and treatment of thromboembolic complications in pregnancy *In* Heparin Chemistry and clinical usage (eds V V Kakkar and D P Thomas) Acad Press London New York 1976
5 Bonnar J & Walsh J Prevention of thrombosis after pelvic surgery by British dextran 70 Lancet *2* 614 1972
6 Coon W Willis P & Keller J Venous thromboembolism and other venous diseases in the Tecumseh Community Health Study Circul *48* 839 1973
7 Daniel D G Campbell H & Turnbull A C Puerperal thromboembolism and suppression of lactation Lancet 2 287 1967
8 Flessa H Glueck H & Dritschilo A Thromboembolic disorders in pregnancy Pathophysiology diagnosis and treatment with emphasis on heparin Clin Obstet Gynaecol *17* 195 1974
9 Friend J R & Kakkar V V Deep vein thrombosis in obstetric and gynecological patients *In* Thromboembolism Diagnosis and treatment (eds V V Kakkar and A J Jouhar) Churchill Livingstone Edingburgh and London 1972
10 Hallböök T Månsson B & Nilsén R A strain gauge plethysmography with electrical calibration Scand J Clin Lab Invest *25* 413 1970
11 Hallböök T & Göthlin J Strain gauge plethysmography and phlebography in diagnosis of deep venous thrombosis Acta Chir Scand *137* 37 1971
12 Hiilesmaa V Occurrence and anticoagulant treatment of thromboembolism in gravidas parturients and gynecological patients A study of 678 cases treated in the

Women s clinic of the University of Helsinki in 1953 1957 Acta Obstet Gynecol Scand Suppl 2 1960
13 Holford C P Graded compression for preventing deep venous thrombosis Brit Med J *2* 969 1976
14 Husni E Pena L & Lenhert E Thrombophlebitis in pregnancy Am J Obstet Gynecol *97* 901 1967
15 Jackson P Puerperal thromboembolic disease in high risk cases Brit Med J *1* 263 1973
16 Jeffcoate T N A Miller J Roos R F & Tindall V R Puerperal thromboembolism in relation to the inhibition of lactation by estrogen therapy Brit Med J *4* 19 1968
17 Ruckley D V Heparin versus dextran in the prevention of deep vein thrombosis A multi unit controlled trial Lancet *2* 118 1974
18 Scurr J H Ibrahim S Z Faber R G & LeQuesne L P The efficacy of graduated compression stocking in the prevention of deep vein thrombosis Brit J Surg *64* 371 1977
19 Whitney R J A measurement of volume changes in human limbs J Physiol (Lond) *121* 1 1953
20 Woodfield D G Cole S Allan A G E & Cash J Systemic fibrinolysis during and following elective cesarean section and gynecological operations J Obstet Gynecol Br Cwlth 79 538 1972
21 Zetterqvist S Ericsson K & Volpe U The clinical significance of biphasic venous emptying curves form the lower limb in venous occlusion plethysmography Scand J Clin Lab Invest *35* 497 1975
22 Åstedt B Significance of placenta in depression of fibrinolytic activity during pregnancy J Obstet Gynecol Br Cwlth *79* 205 1972

Submitted for publication April 4 1978

Agneta Bergqvist M D
Department of Obstetrics and Gynecology
General Hospital
S 214 01 Malmö
Sweden

Acta Obstet Gynecol Scand 58 477 – 480 1979

PREGNANCY AND DELIVERY AFTER CONIZATION OF THE CERVIX

M Grönroos P Liukko P Kilkku and R Punnonen

From the Department of Obstetrics and Gynecology University Central Hospital Turku Finland

Abstract Of 327 patients who had undergone conization of the cervix in 1968 74 in the Department of Obstetrics and Gynecology Turku University Central Hospital 249 replied to a questionnaire Eighty nine of these had had total of 112 pregnancies after conization Conization had only minimal influence on the pregnancies and none on the deliveries Over 90 per cent of the newborns delivered were full term and without anomalies The incidence of spontaneous abor tions also did not differ from normal

With the steep increase in the frequency of diagnosis of dysplasia and Ca in situ of the uterine cervix since the early 1960s detected through masss screening conization has become an increasingly important therapeutic method (1) When the specimen is ex amined serially conization is also a diagnostic pro- cedure A decrease in the mean age of patients with dysplasia and Ca in situ (2 7) increases the propor tion of patients for whom preservation of fertility is important

Conization is known to be adequate treatment for dysplasia and Ca in situ and no significant dif ferences have been reported between the incidence of recurrences when compared with amputation of the cervix or total hysterectomy (6 8) However amputa tion of the cervix is known to increase complications related to pregnancy and parturition and to cause changes in menstruation (4) nearly 10 per cent of the patients had dysmenorrhea hematuria or pyometra caused mainly by cervical stenosis

MATERIAL

The study comprised patients undergoing cervical coniza tion at the University Central Hospital Turku in 1968 74 At the time of conization all patients were ≤36 years old 327 questionnaires were sent out and we received 249 replies Of 78 patients who did not reply to our question naire 0 were lost due to a changed address we were unable to trace eight case histories and therefore the dropout was 50 patients

The age distribution of 89 patients pregnant following conization is presented in Table I Data relating to the pregnancies prior to conization are seen in Table II The majority of the patients were either nulliparous or para 1 Twelve patients had had 1 2 spontaneous abortions and seven patients had undergone legal abortion Table III shows the indications for conization The majority con sisted of dysplasias of different degrees (87 per cent) and the remaining 13 per cent were patients with Ca in situ and cer vicitis

RESULTS

The total number of pregnancies following coniza tion of the cervix was 112 (Table IV) Eight patients had a spontaneous abortion in the first trimester after conization (Table V) Five of them later gave birth to an infant of normal weight one underwent a legal abortion in the eight week Two patients had an abor tion in the second trimester Nineteen patients under went legal abortion by evacuation and curettage and one patient by hysterectomy with sterilization

Nineteen patients had a history of pre-conization abortions (Tables II and VI) One patient with earlier

Table I *Age distribution of 89 patients pregnant following cervical coni ation*

Age (years)	*Number of patients*
≤25	27
6 – 30	38
31 – 35	[illegible]
= 36	2
Total	89

Table II *Pregnancies before conization*

0 – para	20
1 – para	43
2 – para	15
3 – para	8
4 – para or more	3
1 – 2 spontaneous abortions	12
1 legal abortion	5
2 legal abortions	2

Table III *Histopatological diagnosis in 89 patients with coni ation*

Diagnosis	Number of cases	per cent
Cervicitis	5	5
Dysplasia	77	87
Carcinoma in situ	7	8
Total	89	100

Table IV *Number of pregnancies after coni ation*

Spontaneous abortion	10
Legal abortion	20
Ectopic pregnancies	2
Deliveries	80
Total	112

spontaneous abortion used successful contraception one underwent legal abortion eight were delivered of a normal infant weighing over 2 501 g and one patient gave birth to two children of normal weight Only one patient suffered a spontaneous abortion for which the histological diagnosis was blighted ovum Seven women had had one or more legal abortions before conization Two of these used successful contraception throughout the post-conization period three patients were delivered of an infant of normal weight and two had a spontaneous abortion The histological diagnosis in one case was a blighted ovum

Sixty nine patients had a total of 80 deliveries after conization fifty nine women had one delivery nine had two and one three One infant weighing under 1 501 g was delivered by a patient who had undergone conization in the 27th week of pregnancy (Table VII) The delivery took place two weeks after the coniza and the infant weighed 830 g Ten patients red infants weighing 1 501 2 500 g at birth In one of these cases conization was undertaken twice a the process had continued beyond the specimen on case involved a dead fetus associated with antibodies one infant had a serious congenital heart disease an one case was a twin pregnancy The gestational age of newborns was recorded as over 36 weeks in 7 cases 33 36 weeks in six cases and 28 32 weeks in on case

During pregnancy 31 patients had light uterine con tractions and 14 of these noted spotting of a few day duration as well (Table VIII) Twenty one patient were sent on a short sick leave during their pregnanc because of the potential risk Twenty seven of the 3 patients with relative complications of pregnanc were delivered of a full term infant weighing ove 2 501 g Three newborns weighed 1 501 2 500 g an the only newborn weighing under 1 500 g also belong ed to this group

Only a few complications were observed durin delivery (Table IX) There was not a single case o precipitate labor Normal deliveries totalled 76 breech presentations were nil with the exception o one twin delivery in which the second twin wa

Table V *Spontaneous abortion after conization and the fate of pregnancies after spontaneous abortion*

Trimester	No of spontaneous abortion	Fate of the pregnancies subsequent to spontaneous abortion: Legal abortion	Normal delivery
1st	8	1	5
2nd	2	–	–

Table VI *Pregnancies after conization in those patients who had had abortions before conization*

Before conization		After conization: Spontaneous abortion	Legal abortion	One normal delivery	Two normal deliveries	Contraception
Spontaneous abortion	12	1	1	8	1	1
Legal abortion	5	1+1	–	2	–	1
Legal abortions	2	–	–	1	–	1
Total	19	3	1	11	1	3

Blighted ovum

Table VII *Weight distribution of 81 newborns*

Weight (g)	No of newborns
≤1 500	1
1 501–2 500	11
≥2 501	69
Total	81

Table IX *Deliveries after conization*

	No of cases	Per cent of total
Normal delivery	76	95
Breech delivery	–	–
Vacuum extraction	1	1
Twins	1	1
Cesarean section	2†	3
Total	80	100

Maternal exhaustion
† Indications
a) Pelvis angusta cum precentatio cl [illegible]
b) Sectio antea et pro sterilisatione

delivered as a breech Vacuum extraction had to be used once on account of the mother s exhaustion Two cesarean sections were performed one for a narrow pelvis and breech presentation and the other because of an earlier cesarean section and sterilization

Conization appeared to affect menstrual pain relatively little 79 per cent noticed no change 10 per cent felt better and 11 per cent felt slightly worse

The most popular of the contraceptive methods employed after conization were oral combined pills (35 per cent) IUD (31 per cent) condom or foam (18 per cent) and the minipills (4 per cent) Other contraceptive methods were used in 12 per cent

The study included two patients with ectopic pregnancy one during minipill contraception and the other while the patient was using a copper IUD

DISCUSSION

Steeply rising frequency of diagnosis of premalignant and malignant lesions of the uterine cervix during the 1960s (1) and the steadily falling mean age of these patients during the 1970s (2 7) give increasing grounds for consideration of a modified operation to ensure later fertility Earlier studies have indicated that conization does not influence conception to any appreciable extent (3)

We were unable as Kullander and Sjöberg (5) to demonstrate any significant post-conization changes in the patient s condition during pregnancy or at delivery Over 90 per cent of the deliveries ended in the birth of a normal full term well grown newborn The number of spontaneous abortions was even slightly below usually reported The frequency of legal abortions is fairly high and hence attention should be paid to post-conization contraception at the beginning of follow up visits

It has been shown earlier that the results obtained after conization do not differ from those following amputation of the cervix or hysterectomy (6 8) and so it can be recommended as both a diagnostic and therapeutic method for patients in whom it is desirable to preserve fertility

REFERENCES

1 Grönroos M Tyrkkö J Järvi O & Rauramo L Experience of a continuing mass screening programme Ann Chir Gynaecol Fenn 63 470 1974
2 Grönroos M Liukko P Punnonen R & Rauramo L Etiology of premalignant lesions in teenagers Acta Obstet Gynecol Scand in press
3 Holzer E Fertilität Schwangerschaft und Geburtsverlauf nach Konisation der Portio vaginalis uteri Geburtsh u Frauenheilk 3? 950 1972
4 Karjalainen O Aito M & Timonen S Sequelae of combined amputation and conisation of the cervix Ann Chir Gynaecol Fenn 63 160 1974
5 Kullander S & Sjöberg N-O Treatment of carcinoma in situ of cervix uteri by conisation A five year follow up Acta Obstet Gynecol Scand 50 153 1971
6 Liukko P Punnonen R & Grönroos M Carcinoma

Table VIII *Complications during pregnancy and weights of newborns*

Complication	No of cases	Weight (g) <1 500	1 501–2 500	≥2 501
Spotting	14	1†	–	13
Light contractions	31	–	3	14

All the patients with spotting had also light contractions
† Conization was performed during the pregnancy

in situ cervicis uteri diagnosis treatment and prognosis Int J Gynaecol Obstet *15* 494 1978
7 Punnonen R Grönroos M & Peltonen R Increase of premalignant cervical lesions in teenagers Lancet *1* 949 1974
8 Wolf W Baltzar J Schekatz E & Lohe K Die Rezidiv frage des Carcinoma in situ der Cervix Geburtsh u Frauenheilk *35* 37 1975

Submitted for publication June 6 1978

M Grönroos M D
Department of Obstetrics and Gynecology
University Central Hospital
SF 20520 Turku 52
Finland

Acta Obstet Gynecol Scand 58 481 – 483 1979

EFFECT OF ALTHESIN ANESTHESIA ON BLOOD LOSS DURING THERAPEUTIC ABORTION

A comparison with local and thiopental anesthesia

Birger R Møller Søren Mommsen Niels Bo Bøggild Madsen Torben Bo Vestersgaard Andersen Andrew Olcott and Jørgen Trier Hansen

From the Surgical Out Patient Clinic and the Department of Anesthesia Aarhus Kommunehospital Aarhus Denmark

Abstract During recent years the use of steroid anesthesia has rapidly increased In our hospital a number of surgical procedures have been performed under Althesin[R] anesthesia and in some cases the peroperative bleeding seemed to be rather profuse Blood loss was studied in 90 healthy women in the first trimester of pregnancy undergoing therapeutic abortion using different types of anesthesia

The patients were divided into three equal groups according to the duration of pregnancy In each group 10 patients underwent operation under local anesthesia 10 under thiopental anesthesia and 10 under Althesin

In all three groups blood loss was the smallest when local anesthesia was used (Fig 1) Amounting to only one third to one half of that occurring under thiopental anesthesia Under thiopental anesthesia the blood loss gradually increased with increasing gestational age with moderate variations Alternatively in this investigation Althesin anesthesia was characterized by pronounced blood loss particularly in the ninth and tenth weeks of pregnancy and in some cases by rather profuse bleeding

We find that Althesin anesthesia should be used for gynecological surgery only in departments which are equipped to control profuse bleeding and possible cardiovascular complications

During recent years the use of steroid anesthesia has rapidly increased Such anesthetics are particularly recommended for short procedures (8 13) such as therapeutic abortions and endometrial curettage In our hospital a number of surgical procedures have been performed under Althesin[R] anesthesia and in some cases the peroperative bleeding seemed to be more profuse The purpose of this study was to examine the effect of Althesin anesthesia on blood loss during therapeutic abortions as compared with that occurring during local and conventional general anesthesia

MATERIAL AND METHODS

The series consisted of 90 women in the first trimester of pregnancy undergoing therapeutic abortion All the women were nulliparous their ages ranged from 15 to 39 years and averaged 24 2 years The gestational age was estimated clinically by the obstetrician on the basis of the menstrual history and the size of the uterus

All the operations were performed as on out patient by the same doctor an experienced gynecologist In all cases the procedure was dilatation by Hegar s method followed by vacuum aspiration This procedure has previously been described in detail (10)

The patients were divided into three equal groups according to the duration of pregnancy as follows group I duration less than 9 weeks group II 9 10 weeks group III 11 12 weeks In each group 10 patients underwent operation under Althesin anesthesia 10 under thiopental anesthesia and 10 under local anesthesia

Informed consent to the procedure was obtained from all the patients concerned

Althesin anesthesia No premedication was given The anesthesia was induced by i v Althesin 0 5 ml per 20 sec until loss of the ciliary reflex Small increasements of 1 2 ml were administered during anesthesia The total amount of Althesin given was approximately 0 1 ml/kg The anesthetic was supplemented with inhalation of a 2 1 mixture of nitrous oxide and oxygen Postoperatively pethidine 25 mg i v was given

Thiopental anesthesia All the patients were premedicated with diazepam 10 mg i v and anesthesia was induced with i v injections of atropine 0 5 mg tubocurarine 3 mg and a dose of thiopental 250-300 mg Small doses of pethidine 20-40 mg were administered as an analgesic Anesthesia was maintained by sufficient additional thiopental and in a few cases with small doses of succinyl holine and inhalation of a 2 1 mixture of nitrous oxide and oxygen

Local anesthesia Diazepam 10 mg was given i v as premedication The local anesthetic for paracervical blockade (1 per cent lidocaine + 0 005 per cent adrenaline 10 + 10 ml) was injected at the junction of the cervix and vagina in the lateral fornices in the 4 and 8 o clock positions The needle was inserted 10 mm into the tissue the syringe aspirated and then 10 ml of the solution was injected on either side of the cervix

Postoperatively all patients were given methyl-ergonovine maleate (Methergine[R]) 0 2 mg i m

Blood loss during operation During the suction procedure the uterine contents were collected in a container After the operation a known amount of 5 per cent sodium hydroxide was added to the container and 24 hours later the optical density of the resulting alkaline hematin solution was measured This result was compared with a venous blood sample from the patient prepared similarly The principle of

this method was described by Hallberg & Nielsson (7) and modified by Kasonde & Bonnar (9) Blood loss on drapes and sponges was minimal and therefore disregarded

RESULTS

The results are shown in Fig 1 Mann Whitney s test was used in the statistical analysis There is a highly significant statistical difference ($p<0\ 05$) between the subgroup of local anesthesia and that of Althesin anesthesia within all three groups designated according to duration of pregnancy and also ($p<0\ 05$) between the subgroups of local and thiopental anesthesia In contrast there was no statistical difference in blood loss between the two types of general anesthesia except in group II which showed a significantly higher ($p<0\ 05$) blood loss when Althesin was used being almost twice as large as under thiopental anesthesia It is remarkable that Althesin anesthesia was also associated with a wide range in blood loss particularly in group II (40 300 ml)

DISCUSSION

In 1941 Hans Selye reported anesthetic effects of steroid hormones (12) Since then many attempts have been made to develop a steroid product which could be used as an alternative to the common anes During recent years Althesin has been intro- as a highly satisfactory induction agent and is as the main anesthetic for short pro res because as the manufacturers say it has a notably wide margin of safety and little local irritation it gives prompt smooth induction and rapid recovery normally free from hangover effect (6)

In our hospital we have for several years performed nearly all therapeutic abortions under local anesthesia This method is rapid reliable and adequate for most patients (10) In a few cases legal abortions have been performed under general anesthesia produced by thiopental As previously reported (11) we had found that blood loss under local anesthesia was only one half of that occurring under general anesthesia On that background we decided to change to Althesin for general anesthesia

In many respects Althesin is an attractive anesthetic for therapeutic abortion The induction into sleep has been described as quicker and more comfortable for the patients and recovery as more complete and rapid than after thiopental (1) Allegedly no damage to the veins should occur (12) Althesin has been characterized as a very safe intravenous anesthetic mostly because it should prove difficult to give an overdose (2 5) Some investigators have recommended it for anesthesia in out patient clin cs (3 4) and for gynecological surgery (1) However as far as we know the effect of Althesin on blood loss during intrauterine operations has not previously been reported

In the present study the blood loss in all three groups was smallest when local anesthesia was used Generally the bleeding here was only one third to one half of that occurring under thiopental anesthesia Blood loss under Althesin anesthesia varied within wide limits particularly in group II where it was nearly twice as large as that occurring under thiopental anesthesia and three times that under local anesthesia ranging from 40-300 ml In two patients the

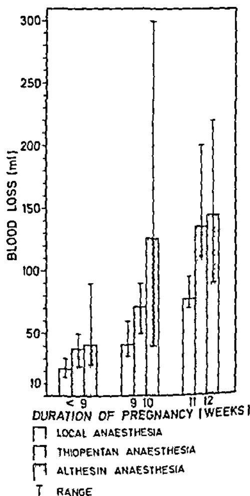


Fig 1 Blood loss during therapeutic abortion in 90 first trimester pregnancies

blood loss during operation was close to 300 ml

The bleeding was well tolerated by all the patients studied but the occurrence of profuse hemorrhage as was seen in some of the patients under Althesin anesthesia may very well hazardous to a patient with a limited cardiovascular reserve

CONCLUSION

It may be said that the blood loss during therapeutic abortion depends upon the anesthesia used We find that local anesthesia is well suited for short gynecological procedures and blood loss is reduced to a minimum Under thiopental anesthesia the blood loss gradually increases with increasing gestational age with only moderate variations In this study however Althesin anesthesia was characterized by a pronounced blood loss particularly in the ninth and tenth weeks of pregnancy and in some cases rather profuse bleeding

We find that Althesin anesthesia should be used for gynecological operations only in departments which are equipped to control profuse bleeding and possible cardiovascular complications

REFERENCES

1 Benke A Gogolak G Stumpf Ch & Tschakaloff Ch Comparative experimental and clinical studies of CT 1341 and hydroxydione Anesthesist *21* 344 1972
2 Bradford Elizabeth M W Miller D C Campbell D & Baird W L M CT 1341 interaction with some anaesthetic agents Br J Anaesth *43* 980 1971
3 Campbell D Steroid Anaesthesia An appraisal of Althesin (CT 1341) Anaesthesist *21* 336 1971
4 Campbell D Forrester A C Miller D C Hutton I Kennedy J A Lawrie T D V Lorimer A R & McCall D A preliminary clinical study of CT 1341 A steroid anaesthetic agent Br J Anaesth *43* 14 1971
5 Campbell D Miller D C & Bradford Elisabeth M W Althesin further studies of interaction with anaesthetic agents Postgrad Med J June supplement 123 1971
6 Glaxo Laboratories Limited Althesin Intravenous anaesthetic Division Greenford Middlesex 1974
7 Hallberg L & Nielsson L Determination of menstrual blood loss Scand J Clin Lab Invest *16* 244 1964
8 Heinonen J Orko Riitta & Louhija A Anaesthesia for cardioversion A comparison of Althesin and thiopentone Br J Anaesth *45* 49 1973
9 Kasonde J M & Bonnar J Effect of sterilisation on menstrual blood loss Br J Obstet Gynaecol *83* 572 1976
10 Møller B R Hansen J T Diedrich P & Oram V Therapeutic abortion in an out patient clinic Acta Obstet Gynecol Scand *57* 41 1978
11 Møller B R Hansen J T & Mommsen S Effect of general and local anaesthesia on blood loss during and after therapeutic abortion Acta Obstet Gynecol Scand *5* 131 1978
12 Selye H Anaesthetic effects of steroid hormones Proceedings of the Society for Experimental Biological Medicine *46* 116 1941
13 Warren J B Althesin in the dental chair Postgrad Med J June Supplement 130 1972

Submitted for publication April 4 1978

Birger R Møller M D
Miltonsvej 11
DK 8270 Højbjerg
Denmark

Acta Obstet Gynecol Scand 58 485–490 1979

PREGNANCY COMPLICATIONS FOLLOWING LEGALLY INDUCED ABORTION

Erik B Obel

From the Department of Obstetrics and Gynecology YA and the Laboratory of Pediatric Pathology University of Copenhagen and the Department of Gynecology Frederiksberg Hospital Copenhagen Denmark

Abstract The frequency of pregnancy and delivery complications in women whose previous pregnancy had been terminated by a legally induced abortion is evaluated in a prospective and a retrospective study

Bleeding before 28 weeks of gestation and retention of placenta or placental tissue occurred more frequently after legal abortion than in a control group matched for age parity and socio-economic status

Other pregnancy and delivery complications did not occur more frequently after legal abortion It is of particular interest that the study could not demonstrate an increased frequency of low birth weight among women whose previous pregnancy had been terminated by legal abortion

In 1972 an epidemiological study from Hungary (6) suggested that a history of an induced abortion was correlated with an increased frequency of prematurity Women with no previous abortion had a frequency of prematurity of 10 1 per cent compared with 16 1 per cent 19 7 per cent and 27 0 per cent for women with 1 2 3 or more induced abortions respectively There was however no evidence of a causal relationship between abortion and subsequent prematurity and a history of induced abortion is frequently linked with characteristics such as age smoking and socio-economic status which are already known to be associated with an increased incidence of low birth weight

The present paper concerns two studies one prospective the other retrospective designed to evaluate whether women with a previous legally induced abotion have an increased frequency of complications of pregnancy and delivery when compared with controls For the first study it is possible to describe in detail the maternal characteristics of the comparable groups Obel (10)

The data were collected as part of the W H O study of the long term sequelae of induced abortion

MATERIAL AND METHODS

Prospective study The study includes all the 7 327 women who were registered in the period 1st April 1974 to 31st December 1975 for delivery in two Copenhagen hospitals The Rigshospitalet is a hospital which acts as a referral centre for patients with pregnancy complications from the whole of Denmark whilst Frederiksberg Hospital provides a general maternity service for a part of Copenhagen

All women in the study were contacted at their first contact with the hospital which in 83 per cent was before the 24th week of gestation All patients were interviewed by specially employed and trained staff

The following data were collected Age occupation of the woman and her partner education date of last menstrual period smoking habits medication previous diseases previous surgery on the reproductive organs previous pregnancies and their outcome last type of contraception whether pregnant while on contraception whether pregnancy planned and complications during the present pregnancy

After the first interview the data were entered on a structured form and eventually computed by WHO in Geneva Four categories were then described

Group 1 Women whose last pregnancy was terminated by legal abortion (576 women)

Group 2 Women whose last pregnancy ended in spontaneous abortion or stillbirth (1 009 women)

Group 3 Women whose last pregnancy ended in a live birht (2 900 women)

Group 4 Women with no previous pregnancies (2 775 women)

For every patient in group 1 one or two control subjects were matched in the following way

Group 1 parity 0 – *Group 3* parity 1 Matched for age (5 year groups) and socio-economic status

Group 1 parity 0 – *Group 4* Matched for age (5 year groups) and socio-economic status

Group 1 parity >0 – *Group 3* Matched for age (5 year groups) socio-economic status and parity

A second interview of all women in groups 1 and 2 as well as matched patients in groups 3 and 4 was conducted at about 28 weeks of gestation when the following data were collected smoking habits medication pregnancy complications X ray ultrasound operation or vaccination during pregnancy and working conditions

Between 91 and 94 per cent of those selected attended the second interview

After delivery pregnancy and delivery complications were registered on the basis of the previous interviews as well as of the patient records from the two departments

The following groups were compared

Group 1 1 Women in group 1 with only one previous pregnancy terminated by legal abortion

were compared with

Group 2 1 Women in group 2 with only one previous pregnancy ending in spontaneous abortion (not matched)

Group 3 1 Women in group 3 with only one previous pregnancy ending with delivery of a living child (Matched for age and socio economic status)

Group 4 0 Women with no previous pregnancies (Matched for age and socio-economic status)

Besides the entire group 1 was compared with

Group 5 Women from groups 3 and 4 (Matched for age parity and socio-economic status)

Examination of placenta A histological examination of placenta was carried out in a random sample of patients of group 1 with one previous pregnancy and matched patients of groups 3 1 and 4 0 This examination could not be carried out on the total population because of lack of resources

Retrospective study The retrospective study comprises a total of 6 771 patients registered for delivery from 1st April 1967 to 1st April 1973 at the maternity ward YA of Rigshospitalet The basis of the study is records transferred to punched cards The following information was available Age parity number of pregnancies and their outcome delivery complications and birth weight

In the retrospective study only women with one previous pregnancy terminated by a legally induced abortion were studied The control groups were obtained by matching for (5 year groups)

following matched groups were compared

ıp 1 1 Women with only one previous pregnancy inated by legal abortion

compared with

Group 2 1 Women with only one previous pregnancy ending in spontaneous abortion

Group 3 1 Women with only one previous pregnancy ending with delivery of a living child

Group 4 0 Women with no previous pregnancies

STATISTICS

When testing of matched pairs McNemar s test should be adopted (2)

This test implies that the features to be examined is listed for both members of the matched pair If the feature to be examined was listed for only one of the individuals in the pair both were excluded from the analysis This can seriously reduce the available material It was decided to test the marginal distributions for the total data by means of X^2-test and then test selected parameters by McNemar s test 5 per cent was regarded as the level of significance When the expected number of the individual categories was lower than 5 Fisher s exact test was adopted and 2 5 per cent regarded as the level of significance as the test is one tailed

It was not possible to find match patients for all patients in group 1 and the number of matched pairs differs according to the control group

In the retrospective study it was impossible to identify the individual patient of the matched pair So this part of the trial was tested by comparing the marginal distributions by means of X^2-test

In many ways patients suffering from diabetes mellitus and patients with twins display pregnancy patterns different from normal pregnancies In order to avoid their influence on the results these patients as well as patients with spontaneous abortion were excluded from the analysis but not until matching had been accomplished

RESULTS

Prospective study The results of the prospective study appear in Table I

No comparison revealed an increased rate of birth weights below 2 001 grams or 2 501 grams in group 1 Likewise the rate of deliveries before 33 and 3ı weeks of gestation respectively was not higher in group 1 than in the control groups Only when the whole group 1 was compared with group 5 was the number of women who delivered before 37 weeks of gestation higher in group 1 than in the control group This finding is strange since there is no corresponding increase in the frequency of low birth weight It must be noted that in this work gestational age was calculated only from the last menstrual period independent of the menstrual pattern

Table I shows that bleeding before 28 weeks of gestation occurred more frequently in group 1 1 than in groups 4 0 and 3 1 and also in group 1 when this whole group entered the comparison There was no difference between groups 1 1 and 2 1 The frequency of bleeding after 28 weeks of gestation did not differ between group 1 1 and the entire group 1 on the one hand and the control groups on the other The number of patients with insufficiency of the cervix and insufficiency of the placenta was small and there were no differences between groups compared

Retention of placenta or placental tissue at delivery was recorded more frequently in group 1 1 than in group 4 0 and also when group 1 was compared with group 5

All groups compared were analysed for differences of the descriptive variables not used as matching criteria

The following important differences between groups compared were found

There were significantly more smokers in group 1 1 (60 4 per cent) than in group 4 0 (46 0 per cent) and

Table I *The frequency of low birth weight short gestation bleeding during pregnancy retention of placenta or placental tissue insufficiency of the placenta and insufficiency of the cervix in women whose previous preg nancy was terminated by legally induced abortion group 1 and in controls grouped according to the outcome of the previous pregnancy Group 2 1 Last pregnancy ending in spontaneous abortion Group 3 1 Last preg nancy ending in deliverv of a living child Group 4 0 No previous pregnancies Group 5 Either no previous pregnancy or last pregnancy ending in delivery of a living child (Prospective study)*

	Group															
	1 1		2 1		1 1		3 1		1 1		4 0		1		5	
No of previous pregnancies	1		1		1		1		1		0		n		n	
No of previous deliveries	0		0		0		1		0		0		m		m	
No of patients	280		355		223		217		280		273		552		545	
Birth weight																
Less than 2 001 g	5	1 8%	6	1 7%	5	2 3%	2	0 9%	5	1 8%	4	1 4%	12	2 2%	12	2 3%
Less than 2 501 g[a]	16	5 7%	30	8 6%	14	6 3%	8	3 7%	16	5 7%	10	3 7%	38	6 9%	28	5 2%
Gestation at delivery																
Less than 33 weeks	6	2 4%	4	1 2%	5	2 5%	1	0 5%	6	2 4%	1	0 4%	13	2 6%	9	1 8%
Less than 37 weeks[a]	19	7 6%	17	5 1%	17	8 5%	12	5 6%	19	7 6%	12	4 7%	46	9 3%	26	5 2%
Bleeding before 28 weeks of gestation[a]	55	19 6%	81	22 8%	44	19 7%[b]	23	10 6%	55	19 6%[b]	33	12 1%	119	21 6%[b]	79	14 5%
Bleeding at 28 weeks of gestation or later[a]	8	2 9%	9	2 5%	6	2 7%	5	2 3%	8	2 9%	11	4 0%	13	2 4%	14	2 6%
Retention of placenta or placental tissue[a]	18	7 2%	16	5 4%	14	7 0%	8	4 1%	18	7 2%[b]	6	2 5%	39	8 0%[b]	18	3 8%
Insufficiency of the cervix	0		2	0 6%	0		0		0		0		1	0 2%	5	0 9%
Insuffi iency of the placenta	3	1 1%	13	3 7%	1	0 4%	2	0 9%	3	1 1%	9	3 3%	12	2 2%	15	2 8%

a The variable tested by M Nemar s test
b The d fference is sign f cant $p < 0\ 05$
≥ 0
$m \geq 0$
Patients for whom nformat on is not a ailable are excluded fr m th analysis of the relevant ariables

group 3 1 (46 1 per cent) Also in the entire group 1 the number of smokers was greater (63 1 per cent) than in group 5 (52 1 per cent)

The number of patients with more than three previous pregnancies was higher in group 1 than in group 5 24 4 as against 8 4 per cent Furthermore more patients in group 1 (5 4 per cent) had reported other gynecological operations than in group 5 (2 8 per cent)

Smoking the number of previous pregnancies as well as previous gynecological operations have been *found to correlate with low birth weight Obel (10)* Although smoking was more frequent in group 1 1 as well as in the entire group 1 and the entire group 1 was loaded with women with many previous pregnan cies as well as women with previous surgery on the reproductive organs a corresponding increase in the number of children with low birth weight could not be demonstrated in these groups

In group 1 1 13 8 per cent were under 20 years of age and 2 8 per cent over 35 years The equivalent figures in group 2 1 were 3 7 and 5 6 per cent Thus group 2 1 included more patients presenting greater risk of prematures Obel (10) Still there was no dif ference as regards prematurity between groups 1 1 and 2 1

Retrospective study Table II shows the results of the retrospective study The only difference demonstrat ed was when group 1 1 was compared with 2 1 the rate of birth weight beneath 2 001 grams being higher in the latter group It is not possible to give a reason for this as no more characteristics of the patients in group 1 1 and 2 1 are available

Examination of placenta Placenta from 61 patients in group 1 1 61 matched patients in group 3 1 and 55 matched patients in group 4 0 were studied

The frequency of white infarction subchorionic fibrine deposit and intervillous thrombosis did not

Table II *The frequency of low birth weight and retention of placenta or placental tissue in women whose previous pregnancy had been terminated by legally induced abortion group 1 1 and matched controls grouped according to the outcome of the previous pregnancy Group 2 1 Last pregnancy ending in spontaneous abortion Group 3 1 Last pregnancy ending in delivery of a living child Group 4 No previous pregnancies (Retrospective study)*

	Group					
	1 1	2 1	1 1	3 1	1 1	4 0
No of previous pregnancies	1	1	1	1	1	0
No of previous deliveries	0	0	0	1	0	0
No of patients	115	115	135	135	136	136
Birth weight						
Less than 2 001 g	8 6 9%(a)	2 1 8%	9 6 7%	4 3 0%	9 6 6%	7 5 1%
Less than 2 501 g	10 8 6%	10 8 6%	12 8 9%	20 14 9%	12 8 8%	15 11 0%
Retention of placenta or placental tissue	5 4 4%	7 6 0%	5 3 6%	5 3 6%	5 3 6%	1 0 7%

(a) The difference is significant X^2 $p<0\ 05$
Patients for whom information is not available are excluded from the analysis of the relevant variable/s

differ between group 1 1 and the other groups The frequency of lack of cotyledon was significantly higher in group 1 1 than in group 4 0 17 5 and 7 3 per cent respectively No difference was found between groups 1 1 and 3 1 This finding is consistent with an increased frequency of retention of placenta or placental tissue in group 1 1 compared with group 4 0 Table I

The histological findings of the placenta were few group 1 1 contained one patient where funiculitis could be shown seven patients with membranitis four with deciduitis one with Hoffbauer cells one with villus edema and one with villus fibrosis In no case was any difference demonstrated between group 1 1 and groups 3 1 and 4 0 respectively

DISCUSSION

Several studies have reported conflicting results for the correlation between induced abortion and the outcome of a subsequent pregnancy including risk of prematurity The following studies all found a correlation between induced abortion and the frequency of prematurity Von Lembrych (8) and Pantelakis *et al* (11) reported that delivery before 37 weeks gestation was more frequent in women who admitted a previous induced abortion than other women Mariyama & Hirokawa (9) and Papavangelou *et al* (12) demonstrated an increased frequency of induced abortion in women delivering before 37 weeks gestation compared with women delivering after Richardson & Dixon (13) found that wom[illegible] only previous pregnancy had ended in a[illegible] abortion delivered before 37 weeks gestation more frequently than women whose only previous pregnancy had ended in a spontaneous abortion Harlap & Davies (4) found that women with a previous induced abortion delivered children with birth weight less than 2 501 grams more frequently than others The difference among children with birth weight less than 2 001 grams was particularly great

The following investigators however could not demonstrate any differences

Furusawa & Koya (3) and Roth & Aoyama (14) could not demonstrate an increased rate of prematurity in women stating previous induced abortion after adjustment for age and parity Neither could Daling & Emanuel (1) after adjustment for age number of pregnancies spontaneous abortion still birth and socio economic status Hogue (5) found that the frequency of low birth weight was not higher in women whose only previous pregnancy ended in an induced abortion than in women with no previous pregnancies but higher than in women whose only previous pregnancy ended in a delivery The rate of prematurity in the later group was significantly lower than in women whose previous pregnancy ended in an induced abortion

There may be several reasons for the conflicting findings The technique used for the abortion whether the abortion was legal or illegal and whether or not there were normal pregnancies between the abortion and the current pregnancy There may also have been under reporting of previous induced abortions Furthermore women with an abortion history

may be characterized by conditions correlated with prematurity

The factors mentioned above and the ensuing influence on the pregnancies have not been sufficiently described and evaluated in the studies by Furusawa & Koya (3) von Lembrych (8) Mariyama & Hirokawa (9) Papavangelou *et al* (12) Pantalakis *et al* (11) Roth & Aoyama (14) and Richardson & Dixon (13) The results of these studies must be subject to certain reservations

Most of the studies mentioned do not state the abortion technique employed Until now no correlation has been found between abortion technique and prematurity This problem will be discussed in a future study

The studies of Daling & Emanuel (1) Harlap & Davies (4) Pantelakis *et al* (11) and Papavangelou *et al* (12) derive from countries where most abortions are performed illegaly Results from these studies can not be compared automatically with the other studies originating from countries where abortion is legalized The present study only deals with legal abortions

Another complicating factor is whether the pregnancy in question is the first after induced abortion or whether the patient has had several pregnancies between the abortion and the current pregnancy The studies of Furusawa & Koya (3) Hogue (5) von Lembrych (8) and Richardson & Dixon (13) like the present one only deal with pregnancies following immediately after an abortion whereas the other reports include all pregnancies after an induced abortion

The registration of a previous induced abortion may cause problems Some women do not wish to admit a previous abortion resulting in under reporting The present data were therefore compared with data from the central register for legal abortions in Denmark which records all induced abortions in Denmark This register was kept from 1st October 1973 when induced abortion before 12 weeks of gestation was legalized in Denmark This comparison revealed three patients who had not admitted previous induced abortion two of the women were in group 2 and one in group 3 Eight women who had stated that their previous pregnancy had ended in spontaneous abortion were at the time in question registered as induced aborters in the register

Daling & Emanuel (1) have found a different distribution of age and number of pregnancies a greater number of women with low social status and more spontaneous abortions in women stating previous induced abortions than in women without previous induced abortion Harlap & Davies (4) showed that women with previous abortions did not inform about religious affilations as often as others Besides this group of women included more smokers

In order to reduce the confounding effect of such factors Daling & Emanuel (1) used matching Harlap & Davies (4) have adjusted for these factors by multiple regression analysis although this analysis as stated by the authors should not be adopted unhesitatingly for discrete variables mostly available in dichotomized form

By the matching procedure described as well as by an analysis of maternal characteristics in the prospective study an attempt was made to reduce any influence of varying maternal characteristics between groups compared This analysis revealed a greater number of smokers in women stating previous legal abortion than in others Although smoking of cigarettes is correlated with low birth weight Obel (10) an increased number of children with birth weight below 2 501 grams in group 1 could not be demonstrated

It was found that bleeding before 28 weeks of gestation appeared more frequently in women with a previous induced abortion compared with groups 3 1 and 4 0 and 5 but not with group 2 1 Harlap & Davies (4) have previously found that bleeding was more frequent among women with previous induced abortion If the bleeding is caused by the earlier use of instruments which may as shown by Krajl & Lavric (7) and von Seewald (15) leave a scar in the uterine cavity or a synechia this is consistent with the fact that there was no difference in the frequency of bleeding between groups 1 1 and 2 1 Table II Evacuation of uterus was performed in nearly all the patients of both groups in the previous pregnancy

Intrauterine sequelae after induced abortion are also likely to cause an increased rate of retention of placental tissue Table I This increase was demonstrated when women of group 1 1 were compared with women who had not been pregnant before group 4 0 but not when group 1 1 was compared with women who had stated previous deliveries or spontaneous abortion This seems to indicate that the frequency of retention of placental tissue is independent of the outcome of the previous pregnancy

CONCLUSION

This study demonstrated an increased frequency of bleeding before 28 weeks of gestation in women

whose previous pregnancy had been terminated by legally induced abortion Retention of placenta or placental tissue appeared more frequently in women with a previous induced abortion than in women without previous pregnancies

An increased risk of low birth weight or short gestational age could not be demonstrated in women with previous legally induced abortion a result that is consistent with the findings of Daling & Emanuel (1) and Roth & Aoyama (14) These two studies like the present one have aimed at evaluating and adjusting for other differences than the previous induced abortion between women with previous abortions and those without

This study does not totally exclude that induced abortion may influence the risk of prematurity in a subsequent pregnancy but the risk if any must be very small and the material thus not big enough to reveal any difference

REFERENCES

1 Daling J R & Emanuel I Induced abortion and subsequent outcome of pregnancy Lancet *II* 170 1975

2 Fleiss J L Statistical methods for rates and proportions Wiley Interscience New York London Sidney Toronto 197

3 Furusawa J & Koya T The influence of artificial abortion on delivery *In* Harmful effects of induced abortion (ed Y Mariyama) p 74 Tokyo 1966

4 Harlap S & Davies A M Late sequelae of induced ion Complications and outcome of pregnancy and Am J Epidemiol *102* 217 1975

ogue C J Low birthweight subsequent to induced abortion Am J Obstet Gynecol *123* 675 1975

6 Hungarian Central Statistical Office The effect of the number of abortions on premature births and perinatal mortality in Hungary Budapest 1972

7 Krajl B & Lavric V Cervicoistmic incompetence *In* The Ljubliana abortion study 1971 73 (ed L Andolsek) p 2 Ljubliana 1974

8 von I embrych S Schwangerschafts Geburts und Wochenbett verlauf nach künstlicher Unterbrechung der ersten Gravidität Zentralbl Gynaecol *94* 164 1972

9 Mariyama Y L & Hirokawa O The relationship between artificial termination of pregnancy and abortion of premature birth *In* Harmful effects of induced abortion (ed Y Mariyama) p 64 Tokyo 1966

10 Obel E B Pregnancy complications following legally induced abortion An analysis of the population with special reference to prematurity Dan Med Bul *26* 19' 1979

11 Pantelakis S N Papadimitriou G C & Doxiadis S A Influence of induced and spontaneous abortions on the outcome of subsequent pregnancies Am J Obstet Gynecol *116* 779 1973

12 Papavangelou G Vrettas A S Papadotas C & Alexiou D The effect of spontaneous and induced abortion on prematurity and birthweight J Obstet Gynecol Br Comm *80* 418 1973

13 Richardson J A & Dixon G Effects of legal termination on subsequent pregnancy Br Med J *1* 1303 1976

14 Roth L H & Aoyama H Induced abortion and its sequelae Prematurity and spontaneous abortion Am J Obstet Gynecol *120* 868 1974

15 von Sewald H J Holtzhauer R Zschoche E & Kulhavy M Klinische und hysterosalpingographische befinde nach Interruptio Zentralbl Gynaecol *95* 710 1973

Submitted for publication February 1 1978

Erik B Obel M D
Ved Højmosen 138
2970 Hørsholm
Denmark

Acta Obstet Gynecol Scand 58 491–494 1979

DELAYED REPRODUCTIVE COMPLICATIONS AFTER INDUCED ABORTION

Knut Dalaker Sissel Moe Lichtenberg and Gunnar Økland

From the Department of Obstetrics and Gynecology the Central Hospital Stavanger Norway

Abstract An investigation was undertaken regarding subsequent pregnancy in 619 women who had their preceding pregnancy terminated by legal abortion compared with an age and parity matched group of 619 women who continued with the pregnancy to delivery The groups were compared for complications such as first and second trimester abortion cervical incompetence pre term delivery ectopic pregnancy and sterility The total complication rate was 24 3 per cent in the abortion group and 20 2 per cent in the controls No significant difference was found between the two groups for any of the parameters examined except for a significantly higher rate of complications amongst women who had not had a previous delivery 25 5 per cent as opposed to 13 2 per cent in the control group

For the last decade there has been a continuing discussion as to early and delayed complications after induced abortion Early complications found per or postoperatively are easily recognized being more or less a question of definition (6 7) Study of delayed complications however raises ethical problems as well as problems associated with the correct interpretation of findings There are conflicting reports in the literature on the outcome of pregnancy following induced abortion (9 10 12 15)

The aim of this investigation was to compare the outcome of a pregnancy subsequent to an induced abortion with that subsequent to a delivery In this way we can determine if a woman who chooses induced abortion runs a greater risk with respect to her next pregnancy than a woman who delivers normally

MATERIAL AND METHODS

In the late autumn 1976 a questionnaire was sent to all women who had been admitted for legal abortion to the Department of Obstetrics and Gynecology in 19 0-71 72 The control group consisted of an equal number of women who had been admitted to the delivery ward during the same period matched according to age and parity as shown in Table I Women who did not wish to participate in the investigation were asked to return the questionnaire unanswered The questionnaire was worded so that only the authors would know if a women had had a legal abortion i e they were only marked by code number The questions were easy to understand and answer correctly and we offered help if necessary In cases where the questionnaire was returned because of unknown (new) address or if it was not returned at all we either tried to find the information from the patiens records if they had been admitted to the hospital after the abortion/delivery or we obtained information from other hospitals or doctors this also applied if the answers given were incomplete or unclear In the group from which we obtained no information (Table II) we found a slightly higher per cent in the abortion group aged under 18 (13 9 per cent against 9 8 per cent in the controls) Where we received no reply at all information was obtained from hospital records for 59 patients in each group The total complication rate was 27 per cent in the abortion group (24 3 per cent in the total study) and 17 per cent in the controls (total complication rate was 20 2 per cent in the whole study)

We noted the number of women who had had induced or spontaneous abortion before or after the 13th week of pregnancy Incompetent cervix was evaluated clinically and was regarded as a complication if in the subsequent pregnancy it was so short or so open that a cerclage was indicated or if the pregnancy ended with an unexplained late abortion or pre term delivery A *pre term delivery* is here defined as a delivery before the 37th week of gestation and/or the baby weighed less than 2 500 g

Women who complained of sterility after abortion were offered further examination The frequency of ectopic pregnancy was also noted The period of observation in this study was 4-7 years for both groups

RESULTS

The results of the investigation are given in Tables II III and Fig 1–2 Table II shows that we received information from 83 per cent in each group The *total frequency of complications* was in the abortion group 24 3 per cent and in the control 20 2 per cent of the total number of women who tried or succeded in becoming pregnant (Fig I) The difference is not significant If we relate the number of complications to parity we find no difference if the woman had had one or more term pregnancies before the abortion Amongst those not having been pregnant previously the complication rate was 25 5 per cent compared to 13 2 per cent in the controls which is significant at 1 per cent level

Table I *Division in age and parity groups*

Age in years	18	18–24	25–29	30–34	34
No previous pregnancy	1A	1B	1C	1D	1E
One previous delivery	2A	2B	2C	2D	2E
Two or more deliveries	3A	3B	3C	3D	3E

Spontaneous abortion before the 13th week In group 1 (Fig 1) it was particularly early abortion which contributed to the high frequency of delayed complications (9 1 per cent against 3 6 per cent for the controls) In group 3 the figures are 19 2 per cent against 17 9 per cent

Spontaneous abortion after the 13th week The frequency of late abortion revealed no significant difference in the two groups In group 1 we found slightly more late abortions in the abortion group but in group 3 this tendency is reversed

Cervical incompetence and pre term deliveries Even this complication showed very small differences between the two groups however we found that the percentage of women with cervical incompetence or pre term delivery was higher among those who had not delivered a child before their abortion when compared with the control group Again we found the figures reversed if the abortion was performed after one or more deliveries

Ectopic pregnancy We found one ectopic pregnancy each group (Fig 1) but have no further informa to whether these had additional risks e g or the mini pill

ity The frequency of sterility in our investigation was slightly higher for the abortion group than for the controls but the difference is not significant

Complications related to age Fig 2 gives the complications related to age and we found that the percentage was highest in the age group 25 30 years 38 9 per cent against 21 2 per cent in the controls From the Figure we can see that the complication rate in the abortion group increased with age until subgroup C In subgroup D we again found a decrease and an increase in subgroup E The fact that there were fewer patients in these groups could influence interpretation of the results

Complications related to gestational age at abortion Due to the Norwegian Abortion Act there are very few legal abortions undertaken after the 13th week of pregnancy and then only marginally beyond 13 weeks This might be the explanation as to why no significant difference was found when we investigated complications of legal abortion before and after the 10th week of pregnancy (Table III)

DISCUSSION

Neither in the most extensive report we have seen on the consequences of legal abortion The Lane report (12) nor in any other paper we have read have we found coincident investigation of all the complications mentioned above in the same group of patients with matched controls We therefore have to relate our findings to those authors who have examined one or more complications by other means The complication rate in our investigation was 24 3 per cent in the abortion group and 20 2 per cent in the controls this is not statistically significant If the complications are related to parity we found a significant in

Table II *Response to the questionnaire*

	Abortion group		Controls	
Total number of questionnaires	619		619	
Answers received	454	(73 5)	453	(73 5)
Returned without answering	38	(6 0)	5	(1 0)
No information (returned address unknown etc)	68	(11 0)	102	(16 0)
Information from hospital records	59	(9 5)	59	(9 5)
Included for further inv	513	(83 0)	512	(83 0)
Number who tried or succeeded in becoming pregnant again	194	(31 0)	234	(38 0)

The figures within parentheses denote total number in per cent

Table III *Result of the investigation related to length of gestation at time of interruption Complications in per cent of total number who tried to become pregnant Those who had their pregnancies interrupted are not incorporated in the total number except when calculating percentage sterility*

Gestational age at time of interruption	Normal pregnancy and delivery	Interruption of pregnancy	Spontaneous abortion before 13th week	Spontaneous abortion after 13th week	Cervical incompetence pret rm delivery	Sterility	Ectopic pregnancy	Total complications
<10 weeks	63	17	14 (16)	3 (3)	3 (3)	3 (3)	1 (1)	24 (28)
≥10 weeks	65	8	9 (12)	0	4 (5)	4 (4)	0	17 (21)
Total	128	25	23 (13)	3 (2)	7 (4)	7 (4)	1 (1)	41 (24)

The figures within parenthesis denote total number in per cent

crease for those in the abortion group who had not had a delivery prior to the abortion After having had one or more deliveries there was no difference between the two groups

Moriyama and Hirokawa (8) have examined the prevalence of induced abortion in women who had had a spontaneous abortion during the first or second trimester or a pre term delivery They found 32 3 per cent had had a previous abortion whilst in the controls consisting of women who had full term deliveries there where 20 6 per cent with a previous abortion This difference was observed regardless of parity Wright *et al* (14) found 8 spontaneous abortions in the second trimester amongst 91 women with previous induced abortion while in an age matched control group they found just one In our study we found little difference between the abortion group and the controls There appeared to be a slight tendency towards a higher abortion risk in nulliparae but the figures are perhaps too small for such a conclusion Our observed risk in this group is below the expected rate of 15 25 per cent given by other authors (1 5 13)

The Lane report (p 246 a f) refers to investigations from Hungary and Great Britain which emphasize the increased risk of pre term deliveries after induced abortion as do other authors 2 9 10 12 15) but we were unable to confirm this If cervical incompetence is responsible for some of the pre term deliveries our findings relate better to those of Voigt *et al* (11) who did not find *radiological* evidence of cervical damage after induced abortion The ectopic pregnancy rate is also increased after legal abortion

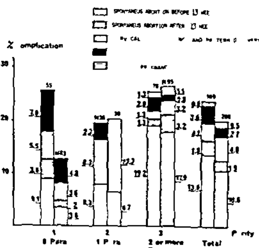


Fig 1 Per cent complications related to parity in the abortion group (controls) according to the total number who tried to become pregnant in each group Those who had their pregnancies interrupted are not incorporated in the total number except when calculating percentage sterility

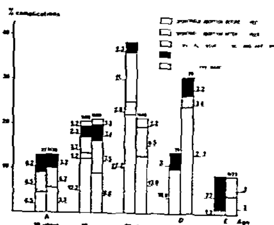


Fig 2 Per cent complications related to age in the abortion group (controls) according to the total number who tried to become pregnant in each group Those who had their pregnancies interrupted are not incorporated in the total number except when calculating percentage sterility

according to some authors while others have found no increase (2 4 12 15) We found one case in each of our groups

We have not found a comparable study concerning sterility after induced abortion Several authors (e g Kahoutek & Laska) have estimated the rate of sterility by comparing the number of women treated for sterility in one area with the number of induced abortions in the same area (3) We found the percentage of sterility to be 3 6 per cent in the abortion group and 2 1 per cent in the control Having completed the investigation we can state that there were very small differences in the incidence of delayed complications after induced abortion when compared with a control group who continued whith their pregnancy It is perhaps important to point out the possibility of an increased risk associated with induced abortion in women who have had no previous deliveries

ACKNOWLEDGEMENTS

This study was supported by grants from Rogalandsforskning and we are also grateful to Amanuensis Tor Bu Rogaland Distriktshøgskole Stavanger for the statistics

REFERENCES

1 Alberman E Elliot M & Creasy R Dhadal Previous reproduction history in mothers presenting with spontaneous abortion Br J Obstet Gynaecol 2 366 1975
rec B & Kupresanin M Vacuum aspiration using acervical bloch for legal abortion as an out patient edure up to the 12th week oif pregnancy Lancet 1 1778 1972
3 Kohoutek Y & Laska L Significance of sterility following artificial interruption of pregnancy Cesk Gynekol 35 398 1970
4 Kotasek A Artificial termination of pregnancy in Czechoslovakia Int J Gynaecol Obstet 9 118 1971
5 Lauritzen J G Genetic aspects of spontaneous abortion Dan Med Bull 24 169 1977
6 Lewis Stella C Lal Shirley Branch B & Beard R W Out patient termination of pregnancy Br Med J 4 606 1971
7 Lichtenberg Sissel Moe Legal svangerskapsavbrytelse Operativ og post operative komplikasjoner Tidsskr Nor Laegeforen 9 566 1974
8 Moriyama Y & Hirokawa T Correlation between induced abortion and premature delivery Snfujin Jissay 15 560 1966
9 Obel E Senfølger efter abortus provocatus Ugeskr Laeger 6 323 1976
10 Roht L H & Hideyasu A Induced abortion and its sequelae Prematurity and spontaneous abortion Am J Obstet Gynecol 7 868 1974
11 Voigt von R Sewald J & Starker K Klinische und Røntgenologische Untersuchungen zur Frage des Zusammenhangs zwischen interruptio und Frü geburt Zbl Gynäk 98 1589 1976
12 Report of the Committee on the Working of the Abortion Act Vol I (Chairman Mrs J Lane) London 1975
13 Research in Reproduction The International Planned Parenthood Federation No 2 1976
14 Wright C S W Campbell S & Beazley J Second-trimester abortion after vaginal termination of pregnancy Lancet 1 1278 1972
15 Wynn M & Wynn A Some consequences of induced abortion to children born subsequently London Foundation for Eduction and Research in Childbearing 7 Walpole Street London S W 3 1972

Submitted for publication May 16 1978

Sissel Moe Lichtenberg M D
Department of Obstetrics and Gynecology
Stavanger Central Hospital
N-4001 Stavanger
Norway

Acta Obstet Gynecol Scand 58 495 1979

SHORT COMMUNICATION

HEAT INDUCTION IN COPPER BEARING IUD S DURING SHORT WAVE DIATHERMY

Niels Chr Nielsen Rene Hansen and Thorkild Larsen

From the Department of Gynecology Bispebjerg Hospital Copenhagen and the Engineering Academy of Denmark Lyngby Denmark

In Denmak copper bearing IUD s are being used to an increasing extent as a contraceptive device About 60 000 were sold in 1977 This increased use has given rise to several unelucidated questions A recurring problem is whether short wave diathermy treatment of women wearing a copper IUD can induce heat in the copper wires which it may be imagined cause local burns As it is extremely difficult to perform direct measurement of a possible rise in temperature in the copper wire *in utero* we set up in collaboration with the Electro department of the Engineering Academy of Denmark a model for calculating the rise if any in temperature

The short wave effects were obtained by placing the patient between two condenser plates measuring 18 27 cm at a distanse of 30 cm and treatment was administered for 20 minutes at 150 W frequency 27 12 MHz

The IUD was located approximately midway between the condenser plates and exposed to a fraction of the short wave effect It was calculated that the maximum effect received would be 106 mW Only a very small part thereof is absorbed by the copper wire as heat the greater part being reflected Calculations showed that the absorbed effect is $3\ 4 \times 10^{-4}$ of that received corresponding to 36 μW

The wire may also and perhaps this is more realistic be regarded as an antenna In general calculations based on a helix antenna are extremely complicated but if the length of the antenna in relation to the wavelength is small it is possible to carry out approximate calculations which are fairly simple Using this principle the effect received was calculated as 6 μW

This calculation presumes that the antenna has not been attuned i e no attempt has been made to bring the antenna into resonance by external components If this had been so the reactive part of the antenna impedance would have been partially abolished and the effect received would increase Measurements and calculations showed that the antenna was not in the vicinity of resonance at 27 12 MHz Thus the maximum effect received by the device is 36 μW On this basis it is possible to calculate how warm the copper wires can become during a conventional treatment of 20 minutes presupposing that the wire does not give off heat to the surroundings This presupposition is of course not fulfilled so that the actual rise in temperature will be considerably less than the 1 6 C found in the theoretical calculations

Moreover the wire will not receive the full 36 μW since part of the effect is absorbed by the tissue before reaching the IUD

Calculations showed a maximum increase in temperature appreciably lower than 1 6 C at the frequencies and duration of treatment used in short wave diathermy of women with pelvic inflammation We therefore felt it was neither reasonable nor necessary to perform investigations *in vivo* We conclude that short wave diathermy does not induce notable heat in the copper bearing device so that there is no indication for removing it before instituting treatment

The detailed calculations are available on request to the authors

Submitted for publication July 27 19 8

N C Nielsen M D
Department of Gynecology
Bispebjerg Hospital
DK 2400 Copenhagen NV
Denmark

Acta Obstet Gynecol Scand 58 497–498 1979

CASE REPORT

UTERINE RUPTURE CAUSED BY MIDTRIMESTER SALINE ABORTION

T K Bryson J L Benumof J R Farina

From the Departments of Anesthesia and Reproductive Medicine of the University of California San Diego La Jolla California U S A

The major medical hazards of chemical abortefacients are intravascular absorption disseminated intravascular coagulation and bleeding from retained products (2 4 6 7 10 11) The major surgical hazards of uterine aspiration and dilatation and curettage are bleeding laceration of the cervix and uterine perforation (4 8 10) Uterine or cervical rupture after pharmacologic induction of midtrimester abortion with prostaglandins $F_{2\alpha}$ or $E_{2\alpha}$ has been noted but rarely (1 3 9) Hypertonic saline administered intra amniotically followed by oxytocin infusion has been reported to result in uterine rupture in a single grandmultiparous (n=11) patient (5) This report documents the first case of uterine rupture following the intra amniotic injection of hypertonic saline followed by oxytocin infusion in a patient of low parity (n=2)

CASE REPORT

The patient was a 20 year old female gravida four para two abortus one and was at 14 weeks gestational age by history and physical examination with an unwanted pregnancy The past history was remarkable for a first trimester abortion three years prior to admission followed by a tubal infection which resolved with antibiotics Two months prior to admission penicillin therapy was given for a positive gonococcal culture from the cervix One and a half months prior to admission bicillin was given for a weakly positive fluorescent treponemal antigen Illicit heroins use was reported in the distant past The patient was otherwise healthy a light smoker with no history of lung or heart disease

On the first day in hospital the patient underwent uneventful amniocentesis with local anesthesia and intra amniotic instillation of 00 ml hypertonic saline (23 4 per cent) One hour later intravenous infusion of pitocin (100 units/500 ml) at nine units/hr was started A sensation of mild uterine cramp was experienced

Twenty six hours later and while the pitocin infusion continued she complained of increased cramplike abdominal pain Examination revealed a temperature of 39 5 C The abdomen was firm tender distended tympanitic with a decrease in bowel sounds At vaginal examination the cer vix was fingertip dilated with membranes intact The uteri was markedly tender with no adnexal masses The supir blood pressure was 130/60 torr with a pulse rate c 140/min In the sitting position there was no palpable puls or blood pressure The hemoglobin concentration was 4 gm per cent with a hematocrit of 14 per cent The pre sumptive diagnosis was probable uterine rupture

At laparotomy findings included approximately three of intraperitoneal blood a uterine rupture in the right co nua and a fetus free floating in the abdomen and sti enclosed in an intact amniotic sac A suprcervical hysterec tomy and right unilateral salpingo-oophorectomy were pe formed The estimated blood loss was five L and was replac ed by four L whole blood and two L D_5RL Pathological e amination of the specimen revealed a markedly attenuate anterior uterine surface through which placental vesse were visible Microscopically areas of placenta accreta u creta and percreta were seen

A stormy postoperative course included adult respirato distress syndrome manifested by arterial hypoxemia an diffuse alveolar infiltrates on the chest roentgenogran Management included Swan Ganz catheterization mecha ical ventilation with positive end-expiratory pressur fibreoptic bronchoscopy and antibiotic therapy Rapi resolution occurred and the patient was discharged twel days later

DISCUSSION

The complications associated with midtrimester ir trauterine instillation of hypertonic saline solution ir clude hemorrhage infection retained products c conception intravascular injection and cervic laceration (2 4 6 7 10 11)

Uterine rupture has been clearly documented i two cases where intra amniotic hypertonic saline an intravenous oxytocin were used to induce abortion (6) In one case the patient was grandmultiparou (gravida 12 para 11) (5) In such patients the dang of uterine rupture at term with oxytocin stimulation well known (1 3 9) In the second case a low uterir rupture was noted two hours after expulsion of th fetus and one hour after digital removal of the retai ed placenta (6)

The case presented now is the first to be documented in which hypertonic saline instillation has resulted in uterine rupture in a patient of low parity prior to the expulsion of the fetus or manual removal of the placenta The details concerning this patient s previous abortion are unknown except that it occurred in the first trimester and was performed vaginally It is unknown what contribution if any abortion might have had in this subsequent abnormal placental implantation but the abnormal implanta tion in all likelihood did contribute to this uterine rupture

Following hypertonic saline instillation unusual ab dominal discomfort orthostatic hypotension and anemia should alert one to the probability of uterine rupture The adult respiratory distress syndrome which occurred in our patient is not an uncommon sequel of intra abdominal hemorrhage and shock This syndrome did not occur in any of the other re ported cases of uterine rupture following the use of chemical abortefacients (1 3 5 6 8 9 10 11)

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the secretarial assistance of Ms Sandra Moed

REFERENCES

Amy J J Complications of prostaglandin induced abortion (Letter) Brit Med J 4 654 1974

…tes W Grimes P A Haber R J Abortion …aths associated with the use of prostaglandin $F_{2\alpha}$ Am J Obstet Gynecol 127 219 1973

3 Fraser I S Complications of prostaglandin induced abortion (Letter) Brit Med J 4 404 1974

4 Glenc F Early and late complications after therapeutic abortion Am J Obstet Gynecol 118 34 1974

5 Horowitz D A Uterine rupture following attempted saline abortion with oxytocin in a grand multiparous pa tients Obstet Gynecol 43 921 1974

6 Kerenyi T D Mandelman N & Sherman D 5 000 consecutive saline abortions Am J Obstet Gynecol 116 593 1973

7 Mackenzie I Z Hillier K & Embrey M P Prostaglandin induced abortions assessment of operative complications and early morbidity Brit Med J 4 683 1974

8 Silverman E M & Rydèn S E Abdominal fetus following induced abortion Am J Obstet Gynecol 122 791 1975

9 Smith A S Rupture of the uterus during prostaglandin induced abortion Brit Med J 1 705 1975

10 Tietze C & Lewit S Joint Program for the Study of Abortion (JPSA) early medical complications of legal abortion Studies Family Plan 3 97 1972

11 Tietze C & Lewit S Early medical complications of abortion by saline Joint Program for the Study of Abortion (JPSA) Studies Family Plan 4 133 1973

Submitted for publication June 15 1978

Jonathan L Benumof M D
Associate Professor of Anesthesia
Anesthesia Research Laboratory M-004
University of California San Diego
La Jolla California 92093
U S A

Acta Obstet Gynecol Scand 58 499–501 1979

CASE REPORT

PREGNANCY IN A NON COMMUNICATING RUDIMENTARY UTERINE HORN

A reason for failed therapeutic second trimester abortion

Rolf Kirschner Tord Löfstrand and Joachim Mark

From the Department of Obstetrics and Gynecology and the Department of Pathology Kärnsjukhuset Skövde Sweden

Abstract Anatomical aberrations in the female genital tract are due to maldevelopment of the Mullerian duct system Various degrees of malformations are described (9) Some of these malformations are discovered during the investigation of amenorrhea persistent dysmenorrhea or infertility while others are discovered in connection with obstetrical problems The incidence of uterine malformations is quoted as 1 1 500–2 000 (8 11) the incidence of uterus unicollis bicornis being as rare as 1 100 000 (3) There is no unified nomenclature for the rarer types of genital malformations Semmens describes a group consisting of functional uteri of single Mullerian origin labelled uterus unicollis bicornus with one rudimentary horn (8) Most rudimentary horns are hollow and allow the expansion of an up to 20 weeks pregnancy (3) Few cases of pregnancy in a rudimentary horn have been seen causing complications during pregnancy and delivery and when performing therapeutic abortions (2 3 4 5 6 1?)

CASE HISTORY

Woman born 1950 Primary oligomenorrhea Basal body temperature and curettage have shown periodic anovulation No history of dysmenorrhea Normal secondary sexual characteristics Married for 7 years after 4 years started investigation for primary infertility During the next year she had two spontaneous pregnancies both ending in abortions with exaereses instrumentalis in the 17th and 8th weeks respectively At neither operative procedure was there any evidence of genital abnormality

The patient was admitted in March 1977 for investigation of a possible missed abortion during a Clomiphene induced pregnancy She was 22 weeks pregnant as judged by observed ovulation on BBT and a positive pregnancy test in the 6th week Uterine growth was normal up to the 19th week when stagnation was noted Fetal heart sounds and fetal movements were not elicited On admission gynecological examination showed slight bloody discharge from a normal closed cervix and the uterus was found to be enlarged corresponding with a pregnancy of approximately 18 weeks

During admission no fetal heart sounds were heard Quantitative HCG initially were 4 000-8 000 IU showing a decreasing trend There was increasing vaginal bleeding and the uterus was decreasing in size Plain X ray of the abdomen showed no signs of fetal skeleton

A diagnosis of uterine fetal death was made and induction of abortion was initiated with extra amnial installation of Rivanol but no more than 100 milliliters could be instilled because of severe pain and reflux The patient was later given a total of two $PGF_{2\alpha}$ infusions producing only sham contractions and considerable pain Uterine status was unchanged and a decision was made to evacuate it

On doing exaeresis the uterine cavity was found to be of nearly normal size yielding sparse normal looking endometrium The uterus was sinistroponated and a relatively mobile rounded fist sized firm tumor was found lying in the right midline position

On laparotomy there was no evidence of intraabdominal hemorrhage The uterus and left adnexa showed normal anatomy On the right side a 10 centimeter diameter tumor was situated in the middle third of what seemed to be the Fallopian tube (Fig 1) The distal third of the tube presented a normal anatomy and was stretched over the tumor a 2 centimeter rupture was seen in the broad ligament What seemed to be the Fallopian tube was inserted at the lower uterine corpus together with a normal round ligament (Fig 1) A normal ovary was present

A provisional diagnosis of an unruptured tubar abortion was made and a right salpingectomy was performed

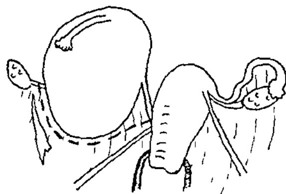


Fig 1 Sketch of the anatomy found at operation Notice the aberrent insertion of the tube and the round ligament on the right side and the slit in the right broad ligament

On incision one found a macerated otherwise macroscopically normal looking male fetus with a 17 millimetres foot length The walls of the tumor resembled myometrium (Fig 2) The removed structure was a thick walled circular mass with a central lumen containing pregnancy products Histologically the wall of the mass showed very thick irregular laminated smooth muscle with a loose appearance The endometrium showed total decidual transformation The findings pointed to an intrauterine pregnancy The laterally attached pencil thick tube showed normal histology

After a study of the literature on uterine malforma a revised diagnosis of a possible pregnancy in a imentary uterine horn was made The material re d was sectioned further especially tangentially its medial end but no signs of tubal tissue were identified No duct or lumen could be demonstrated in the fibrous tissue condensation Hysterosalpingograpy was later performed It showed an anteverted and sinistrodeviated uterine cavity with a normal lining and with normal communication to the left and no signs of luminal connection to the right An intravenous urogram was done to exclude any associated urinary malformations This examination was normal

COMMENTS

Pathological anatomy The anatomical picture mirrors the extent of unilateral maldevelopment of the Müllerian ducts On the affected side one finds in the course of the Fallopian tube a varying sized hollow or solid tumor made up of uterine muscle (1) Laterally it is attached to a normal distal portion of the tube with the fimbriated end closing on to a normal ovary Running between the uterine tissues one finds a condensation of tissue macroscopically looking like the isthmical portion of the Fallopian tube and often attached to the unicorn uterus at an ectopic site This ligamentous tissue is not on histological analysis a normal canalized tube but rather a condensation of the parametrial ligaments traversed by vessels (1 2 3 4 6 8) The round ligament varies in size and point of insertion (1 3 7)

The Wolffian and Müllerian ducts develop embryologically in close connection hence urinary tract malformations of all kinds and severity associated with genital malformations are commonly found

Signs and symptoms Genital malformations with partial or total occlusion will after menarche give a clinical picture of amenorrhea with hematocolpos/metra/salpinx or dysmenorrhea often of a severe kind The dysmenorrhea typical of genital malformations is a primary progressive one quite resistant to therapy and not lessened by parity (2 7 8 10) The symptomatology is worsened by the increased incidence of pelvic endometriosis that develops secondarily and is less severe when it coincides with oligomenorrhea due to a slower build up of menstrual products (8 10) The presence of dysmenorrhea and at the same time the absence of hematometra/salpinx in the uterus unicollis bicornis with a rudimentary horn where in a large proportion of cases there is not tubal communication has been debated because it also has a bearing on the mode of fertilization in these cases Loederslot sees the absence of menstrual blood collection as a proof that a fine channel must exist (5) Semmens cites 50 per cent incidence of dysmenorrhea in his ma erial with this abnormality where the resected blind horn showed a lack of end organ response in some adenomyosis in others and also pressure atrophy with a hemocast (8) These factors possibly explain the scanty signs even when no communication is found As pregnancy occurs in these rudimentary uteri the endometrium must have some capacity for normal activity

Pregnancy in a rudimentary horn is the least common obstetric variety (6 10) and as no communication with the cervix is usual transperitoneal passage of the fertilized ovum or fertilization in the pouch of Douglas must occur This mode of fertilization is described (10) The fate of a rudimentary horn pregnancy is usually disastrous with second trimester rupture clinically resembling that of a tubal ectopic

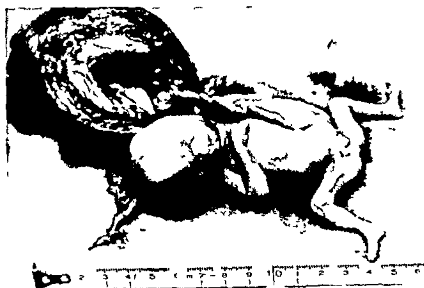


Fig 2 Rudimentary uterine horn displaying thick muscular walls A macerated male fetus was found on opening the cavity

pregnancy (2 6) A few progress to term inside the rudimentary horn mostly as lithopedion while the total fetal salvage including intrauterine as well as secondarily abdominal pregnancies stands at approximately 2 per cent (2 3 6)

As with all other anomalies diagnosis other than retrospectively is difficult The passage of decidual casts from the unicorn uterus together with a diverging palpatory finding is indicative of the condition and past history is helpful in diagnosis as hereditary plays a large part together with the symptoms (4 12) It was earlier diagnosed mostly in connection with complicated pregnancies and births and is presently seen complicating second trimester therapeutic abortions (4)

CONCLUSION

Our patient showed a typical picture of pregnancy in a uterus unicollis bicornis with a rudimentary horn The gynecologist must remember the increased incidence of pathology involving the urinary tract in these patients It is accepted that removal of the rudimentary horn with reimplantation of the round ligament on the uterus is the correct treatment for this anomaly

REFERENCES

1 Beernink F J Beernink H E & Chinn A Uterus unicornis with uterus solidarius Obstet Gynecol *47* 651 1976
2 Jarrel J Effer S B & Mohide P T Pregnancy in rudimentary horn with fetal salvage Am J Obstet Gynecol *127* 676 1977
3 Johansen K Pregnancy in rudimentary horn Obstet Gynecol *34* 805 1969
4 Lauersen N H Wilson K H Zervoudakis I A & Saary Z Management of failed prostaglandin abortion Obstet Gynecol *47* 473 1976
5 Loederslot E W Twin pregnancy in double uterus correspondence Am J Obstet Gynecol *127* 687 1977
6 O Leary J L & O Leary J A Rudimentary horn pregnancy Obstet Gynecol *22* 371 1963
7 Schumacher H B Congenital anomalies of the genitalia associated with unilateral renal agenesis Arch Surgery *37* 586 1936
8 Semmens J P Congenital anomalies of the female genital tract Obstet Gynecol *19* 328 1962
9 Tuchmann Duplessis H & Haegel P Illustrated human embryology Springer Verlag New York 1974
10 Wiersma A F Peterson L F & Justema J E Uterine anomalies associated with unilateral renal agenesis Obstet Gynecol *47* 654 1976
11 Woolf R B & Allen W B Concomitant malformations The frequent simultaneous occurrence of congenital malformations of the reproductive and urinary tract in women Obstet Gynecol *2* 236 1953
12 Zervoudakis I Lauersen N & Saary Z Unusual twin pregnancy in a double uterus Am J Obstet Gynecol *124* 659 1977

Submitted for publication December 12 1978

Rolf Kirschner M D
Department of Obstetrics and Gynecology
Kärnsjukhuset
S-541 01 Skövde
Sweden

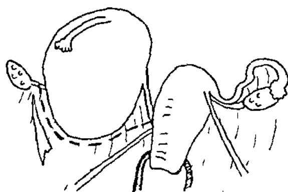


Fig 1 Sketch of the anatomy found at operation Notice the aberrent insertion of the tube and the round ligament on the right side and the slit in the right broad ligament

On incision one found a macerated otherwise macroscopically normal looking male fetus with a 17 millimetres foot length The walls of the tumor resembled myometrium (Fig 2) The removed structure was a thick walled circular mass with a central lumen containing pregnancy products Histologically the wall of the mass showed very thick irregular laminated smooth muscle with a loose appearance The endometrium showed total decidual transformation The findings pointed to an intrauterine pregnancy The laterally attached pencil thick tube showed normal histology

After a study of the literature on uterine malforma a revised diagnosis of a possible pregnancy in a ary uterine horn was made The material re was sectioned further especially tangentially its medial end but no signs of tubal tissue were identified No duct or lumen could be demonstrated in the fibrous tissue condensation Hysterosalpingograpy was later performed It showed an anteverted and sinistrodeviated uterine cavity with a normal lining and with normal communication to the left and no signs of luminal connection to the right An intravenous urogram was done to exclude any associated urinary malformations This examination was normal

COMMENTS

Pathological anatomy The anatomical picture mirrors the extent of unilateral maldevelopment of the Müllerian ducts On the affected side one finds in the course of the Fallopian tube a varying sized hollow or solid tumor made up of uterine muscle (1) Laterally it is attached to a normal distal portion of the tube with the fimbriated end closing on to a normal ovary Running between the uterine tissues one finds a condensation of tissue macroscopically looking like the isthmical portion of the Fallopian tube and often attached to the unicorn uterus at an ectopic site This ligamentous tissue is not on histological analysis a normal canalized tube but rather a condensation of the parametrial ligaments traversed by vessels (1 2 3 4 6 8) The round ligament varies in size and point of insertion (1 3 7)

The Wolffian and Müllerian ducts develop embryologically in close connection hence urinary tract malformations of all kinds and severity associated with genital malformations are commonly found

Signs and symptoms Genital malformations with partial or total occlusion will after menarche give a clinical picture of amenorrhea with hematocolpos/metra/salpinx or dysmenorrhea often of a severe kind The dysmenorrhea typical of genital malformations is a primary progressive one quite resistant to therapy and not lessened by parity (2 7 8 10) The symptomatology is worsened by the increased incidence of pelvic endometriosis that develops secondarily and is less severe when it coincides with oligomenorrhea due to a slower build up of menstrual products (8 10) The presence of dysmenorrhea and at the same time the absence of hematometra/salpinx in the uterus unicollis bicornis with a rudimentary horn where in a large proportion of cases there is not tubal communication has been debated because it also has a bearing on the mode of fertilization in these cases Loederslot sees the absence of menstrual blood collection as a proof that a fine channel must exist (5) Semmens cites 50 per cent incidence of dysmenorrhea in his material w h this abnormality where the resected blind horn showed a lack of end organ response in some adenomyosis in others and also pressure atrophy with a hemocast (8) These factors possibly explain the scanty signs even when no communication is found As pregnancy occurs in these rudimentary u eri th endometrium must have some capacity for normal activity

Pregnancy in a rudimentary horn is the least common obstetric variety (6 10) and as no communication with the cervix is usual transperitoneal passage of the fertilized ovum or fertilization in the pouch of Douglas must occur This mode of fertilization is described (10) The fate of a rudimentary horn pregnancy is usually disastrous with second trimester rupture clinically resembling that of a tubal ectopic

Acta Obstet Gynecol Scand 58 503–505 1979

CASE REPORT

ABSCESS FORMATION OF A GARTNER S DUCT CYST WITH CERVICAL COMMUNICATION IN A CASE OF BICORNUATE UTERUS ASSOCIATED WITH AN IPSILATERAL RENAL AGENESIS

P De Grandi P Janecek and J M Lambercy

From the Department of Obstetrics and Gynecology Centre Hospitalier Universitaire Vaudois Lausanne Switzerland

Abstract One case of abscess formation of a Gartner s duct cyst communicating with the cervix of a bicornuate uterus is presented in a case of ipsilateral renal agenesis The embryonic origin and the incidence of associated genital and urologic malformations are discussed Marsupialization is recommended as an adequate method of treatment

In the female embryo the genital tract evolves from the paramesonephric or Mullerian structures and in the absence of androgenic stimulation the mesonephric or Wolffian system degenerates into vestigial structures consisting of a series of tiny epithelial lined cysts (canals of Gartner) extending from the broad ligament to the vestibulum of the vagina

This development of the genital tract is closely related to that of the urinary system which derives from metanephric structures

As paramesonephric as well as mesonephric and metanephric tissues originate from a common mesodermic intermediate cell mass (the nephrogenic cord) it is not uncommon to observe genital abnormalities associated with renal and/or urologic anomalies

Such a combined abnormality is illustrated by the present report of a case of genital tract malformation associated with unilateral renal agenesis and abscess formation in a Gartner s duct cyst communicating with the endocervix

Two cases of vaginal and cervical communication with mesonephric duct remnants combined with unilateral renal agenesis have been reported by Goldstein and co-workers (1)

Abscess formation in Gartner s duct cyst with vaginal communication in two cases of ipsilateral renal agenesis has been reported recently by Beresford and co-workers (2)

CASE REPORT

A 17 year old female patient with a past history of myelomeningocele successfully operated at the age of 9 months was admitted in May 1977 for chronic vaginal discharge treated unsuccessfully for more than 3 years

At the age of 15 years this regularly menstruating patient had been surgically explored for acute low abdominal pain caused by a hematometra in the left rudimentary horn of a bicornuate uterus which was drained by uterotomy At the time of that operation a urological check up had been performed for a history of recurrent urinary infection The intra venous pyelogram showed a renal agenesis on the left side with morphologically normal kidney and pyeloureteral structures on the right side Renal function was adequate and the micturating cysto-uretroegram did not demonstrate any cysto-ureteral reflux

Two months before her admission in our department the patient had consulted a gynecologist because of a chronic vaginal discharge and he discovered an adnexal mass He decided on a laparotomy which confirmed the presence on the left ovary of a macroscopically and histologically typical endometrial cyst and showed numerous adhesions of both adnexa with the bicornuate uterus and with the Douglas peritoneum After removal of this endometrial cyst the surgeon noticed the presence of a cystic poorly delimited mass located retroperitoneally in the left parameter The puncture of this mass resulted in the aspiration of some gelatinous fluid Three weeks later the patient was complaining of low leftsided abdominal pain and an increase of the vaginal discharge On examination the size of the paracervical cystic mass had increased so she was transferred to our unit

On admission she was afebrile and presented a smelly intermittently vaginal discharge associated with a painful cystic mass 7 cm in diameter located paracervically immediately above the left vaginal fornix Repeated careful speculum examination failed to show any fistulous communication with the vagina but a yellow gelatinous fluid was inconstantly found to be drained from the external os An anaerobic micro-organism (peptococcus) was isolated

As the ipsilateral left renal agenesis and the bicornuate uterus were already known the most probable diagnosis was an abscess formation in a mesonephric Gartner s



Fig 1 Fistulography paracervical cystic cavity with cervical communication admitting an intravenous catheter

cyst partially drained through a cervical fistula This diagnosis was confirmed pre operatively by a very accurate examination of the endocervical wall performed after dilatation under general anesthetic and using a thin hysterometer which revealed the presence of an ostium about 1 5 cm above the external os and admitting a 17 G intra venous catheter The injection of uro through this catheter outlined the cavity of the ical mass (Fig 1) After withdrawal of the the conventionally performed hysterography dem rated the right cavity of the bicornuate uterus but failed to show any passage of the contrast medium in the fallopian tubes as well as in the left uterine cavity which presumably belongs to a rudimentary horn without communication with the cervix as demonstrated by the past history of hematometra (Fig 2)

Concerning the urologic and nephrologic conditions renal function was still adequate and no urinary infection could be found at that time Nevertheless the intravenous pyelogram was repeated and revealed a probable papillary necrosis and a very important cysto ureteral reflux at the micturating time of the examination (Fig 3)

Considering the high degree of vascularization of the wall of this chronically infected cyst as well as the high risk of damage to adjacent organs the treatment consisted in a wide marsupialization of the cyst in the left vaginal fornix The cervix was incised in order to close the cervical communication by resection of the fistula and tracheloplasty In this way the patient became completely free of vaginal discharge and bacterial contamination of the retroperitoneal space could be avoided As a result in a second operation the urologist could safely perform a reimplantation of the ureter in order to correct the cysto-ureteral reflux

COMMENT

According to Semmens (3) the general incidence of female genital tract malformations amounts to about 1 out of 1 800 and approximately 25 per cent of the major abnormalities of the female genital tract are associated with anomalies of the urinary tract

As shown by Müller and associates (4) the frequency of such associations of urinary and/or Wolffian anomalies with genital malformations in the female depends on the degree of failure which occurred in the development or fusion of the Müllerian ducts In cases of fusion of symmetric genital malformations due to a partial or total defect of fusion of the Müllerian ducts an associated urological anomaly is relatively rare Failures of development of one Müllerian system resulting in a hemiuterus with or without controlateral rudimentary horn are associated in 10-20 per cent of the cases with urinary defects In cases of bilateral and symmetrical Müllerian agenesis the rate of associated urinary malformations is much higher

For instance in cases of Rokitansky syndrome characterized by congenital absence of vagina and uterus due to a severe and bilateral defect in the development of the Müllerian systems the incidence of



Fig 2 Hysterosalpingography performed immediately after the fistulography paracervical cystic cavity still filled with contrast medium and right uterine cavity of the bicornuate uterus diagnosed by previous laparotomy Neither the fallopian tubes nor the left uterine cavity corresponding to a rudimentary horn are visualized



Fig 3 Intravenous pyelogram (micturating time) renal agenesis left *important cysto-ureteral reflux right probable* papillary necrosis Sacrococcygeal malformation (past history of operated meningo-myelocele)

concomitant urinary anomaly is reported to be 51 per cent by Phellan and co workers (5) Unilateral renal agenesis associated with this condition was found in 8 out of 71 cases by Miller and Stout (6)

On the other hand in cases of unilateral renal agenesis associated genital malformation in female subjects has been reported (1) in 33 per cent out of 273 case by Hennessey in 9 out of 13 (58 per cent) patients by Selding and even in 90 per cent of the cases studied by Collins

In cases of genital malformation combined with urinary anomalies the defective development of paramesonephric Müllerian and metanephric systems can be associated with abnormal structures evolved from mesonephric Wolffian remnants and resulting in paracervical Gartner s cyst Few cases of such complex malformations have been reported in the literature (1 2) and the one described here seems to be the first to be complicated by abscess formation and cervical communication resulting in a chronic cervical discharge

REFERENCES

1 Goldstein A I Ackerman E S Woodruff R Pogas J Vaginal and cervical communication with mesonephric duct remnants relationship to unilateral renal agenesis Am J Obstet Gynecol *116* 101 1973

2 *Beresford J M George Hyslop P H St Abscess formation in Gartner s duct cysts associated with ipsi lateral renal agenesis A report of two cases* Obstet Gynecol Suppl 49 1977

3 Semmens J P Congenital anomalies of female genital tract Functional classification based on review of 56 personal cases and 500 reported cases Obstet Gynecol *19* 328 1967

4 Muller P Dellenbach P Gillet J Y Les malformations du tractus genital féminin et celles du haut appareil urinaire qui peuvent leur être associée Etude morphologique et physiopathologique *Sem Hop Paris 43* 912 1967

5 Phelan J T Counseller Z S Greene L F Deformities of the urinary tract with congenital absence of the vagina Surg Gynecol Obstet *97* 1 1953

6 Miller N F Stout W Unilateral renal agenesis with congenital absence of the vagina Obstet Gynecol *9* 48 1957

Submitted for publication June 6 1978

P De Grandi M D
Department of Obstetrics and Gynecology
Centre Hospitalier Universitaire Vaudois
Lausanne
Switzerland

Acta Obstet Gynecol Scand 58 507–508 1979

SHORT COMMUNICATION

IN SITU CARCINOMA OF THE UTERINE CERVIX SHOWING SUPERFICIAL ENDOMETRIAL SPREAD

S Gupta I M Gupta and P V Tiwari

From the Departments of Pathology and Prasuti Tantra Institute of Medical Sciences Banaras Hindu University Varanasi India

Abstract Superficial spread of invasive carcinoma cervix over the endometrial surface is extremely rare and may follow radiation therapy (3 5) Ferenczy *et al* (1) have reported an instance of carcinoma *in situ* of ecto cervix spreading on the endometrial surface via the endo-cervical canal This paper reports another *in situ* lesion of the cervix showing superficial endometrial spread

CASE NOTES

A 67 year Hindu female presented with spotty bleeding per vaginum for 10 months with vaginal discharge and low backache She was a multpara and the menopause had occurred seventeen years previously On examination the uterus was small with a palpable right ovary The cervix appeared relatively normal but cytology revealed features of carcinoma *in situ* and a hysterectomy was performed

Pathology Uterus 5x2 5x1 5 cms with tubes and ovary showing a thin atrophic cervix with no gross tumor evident

Microscopically the entire cervical epithelium both of the ecto cervix and endocervix was replaced by tightly packed cancerous squamous cells showing disorganization and a bizarre nuclear pattern with a fair number f mitoses This *in situ* cancerous change was also noticeable in the endocervical glands and had superficially extended to the endometrial surface apparently a migratory phenomena (see legends Figs 1 2 and 3) The endometrial glands in all such areas were themselves not cancerous

COMMENTS

The mechanism of direct superficial spread of carcinoma of the cervix even in cases of invasive carcinoma is subject to controversy Two alternative explanations have been offered (i) Richart Park and Joens and Smith and Townsend (6 8 9) believe that cervical neoplasia begin in a single cell and favor a process of transverse spread by which neoplastic cells are believed to displace and eventually replace the benign epithelium mechanically (ii) Flumen Johnson Reagan Alan and Wentz (2 4 7) on the other hand state that the lesion occurs in a group of cells in a predetermined field and further proliferation and extension of cervical neoplasia is by transformation of cells from normal to malignant in a vertical direction These two possible mechanisms

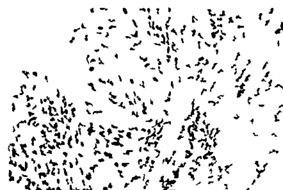


Fig 1 The figure shows squamous cancer cells replacing the surface endometrial layer with isolated normal glands seen in this field Hematoxylin and eosin x160

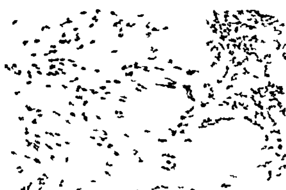


Fig 2 Cancerous squamous cells are seen migrating into the normal endometrial glands Hematoxylin and eosin x160



Fig 3 The figures shows cancerous tissue replacing the en tire superficial endometrial surface with two deeper normal glands showing free cancer cells migrated into their lumina Hematoxylin and eosin x160

may be responsible for the continued superficial spread to the endometrial region The cancer cells in the present case appeared to have extended to the en dometrial surface lining in a creeping manner up wards into an otherwise atrophic and normal en dometrial field

SUMMARY

A case of *in situ* carcinoma of cervix in a postmenopausal woman showing superficial spread
ıum is reported for its rarity and the pos
ı briefly explained

REFERENCES

1 Ferenczy A Richert R M & Okagaki T Endometrial involvement by cervical carcinoma in situ Am J Obstet Gynecol *110* 590 1971
2 Fluman C F Carcinoma in situ and the transitional zone of the cervix Obstet Gynecol *16* 4?4 1960
3 Friedell G H cited from 2
4 Johnson L D The Histopathological approach to early cervical neoplasia Obstet Gynecol Survey *24* 735 1969
5 Kairys L R Dougherty C M & Mickal A Squamous cell carcinoma in situ of the endometrial cavity Am J Obstet Gynecol *88* 548 1964
6 Park I J & Jones H W Clucose-6 Phosphate dehydrogenase and the histogenesis of epidermoid carci noma of the cervix Am J Obstet Gynecol *10?* 106 1968
7 Reagan J W Alan B P & Wentz W B Concepts of genesis and development in early cervical neoplasia Obstet Gynecol Survey *24* 860 1969
8 Richert R M Natural history of cervical intraepi thelial neoplasia Clin Obstet Gynecol *5* 748 1968
9 Smith J W Townsend D E & Sparkes R S Genetic variant of Glucose 6-Phosphate dehydrogenase in the study of carcinoma of cervix Cancer *28* 5?9 1971

Submitted for publication July 27 1978

Saroj Gupta M D
Department of Pathology
Institute of Medical Sciences
Banaras Hindu University
Varanasi – 221005
India

Acta Obstet Gynecol Scand 58 509–510 1979

LETTER TO THE EDITOR

Dear Sir

Cervical neoplasia probably develops through initiating events and promoting agents Virus and spermatozoa might be such an initiating event and repeated viral infections transmitted sexually from male to female and inducing epithelial lesions promoting agents

When discussing the viral etiology of cervical neoplasia three possibilities must be taken into consideration

1 virus is the carcinogen or acts as a co-carcinogen
2 virus may follow neoplastic transformation indicating a greater affinity for cancerous tissue to the virus
3 virus infection and neoplasia are totally unrelated although the frequency of viral infection and cervical neoplasia is significantly higher in Women at risk i e in women with early sexual activity (5)

Naib *et al* (3 4) underline that data from serological studies indicate that herpetic infections *were not newly acquired but instead represented re*currences of latent herpes the initial event probably having occurred months or even years prior the detection of the cervical neoplasia the age prevalence of gential herpes was found to be 5 years earlier in the study population than that of cervical dysplasi and 10 to 15 years earlier than that of CIS Meisels *et al* (1) *state that condylomatous viral lesions are generally present in an younger age group than dysplasia and* CIS both condylomata and cervical neoplasia are directly related to sexual promiscuity and early onset of sexual activity It is conceivable that the immature cervix still covered by fragile epithelium with a *monolayer of cells could be more vulnerable than the* mature cervix

In three interesting papers Naib *et al* (2 3 4) discuss the relation of cyto- and histopathology of genital herpesvirus infection to cervical neoplasia The authors analysed 673 cytologically detected cases of herpes genitalis as to the association of histologically confirmed cervical neoplasia Among these 673 cases there were found 69 women with dysplasia 25 with CIS and 11 with invasive cervical cancer making a total 105 cases (15 6 per cent) of neoplastic and malignant epithelial changes in the uterine cervix

As *important* as studies on the relation of genital herpes virus infection to cervical neoplasia is the evaluation of the occurrence of histologically confirmed viral epithelial lesions usually classified as mild moderate dysplasia (1) within an epithelial area exhibiting atypia of high degree - severe dysplasia and CIS

Figures 1 and 2 show a case of CIS also exhibiting focal viral lesions within undifferentiated in situ carcinoma as sharply demarcated light areas contrasting with the neoplastic epithelium of small and dark undifferentiated cells According to Naib *et al* (4) hypertrophy of the cytoplasm and nucleus of infected cells is usually observed The cells increase in size showing nuclear and cytoplasmic edema this is indicated by the frequent appearance of perinuclear halo as a consequence of the shrinkage of the enlarged nucleus and cytoplasm due to the dehydration of the cell during fixation and staining The nucleoli also enlarge and become vacuolated The nuclear *chromatin is displaced to the perifery and results in* the central nuclear clearing and multinucleation is also seen In the nuclei granules appear to condense and form in the center of the nucleus intranuclear inclusions surrounding by a more or less prominent

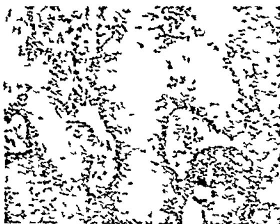


Fig 1 × 1 0 (see text)

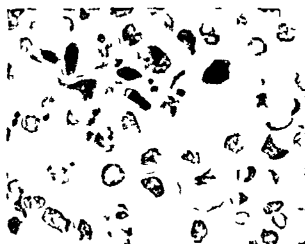


Fig 2 x 380 (see text)

halo The infected cells exfoliate rapidly and usually produce abundant cervical smears Degenerative changes are seen in the cytoplasm and nuclei (vacualization ballooning and bizarre shapes)

REFERENCES

1 Meisels A Fortin R & Roy M Condylomatous lesions of the cervix II Cytologic Colposcopic and Histopathologic study Acta Cytol *21* 379 1977
2 Naib Z M Nahmias A J & Josey W E Cytology and histopathology of cervical herpes simplex infection Cancer *19* 1026 1966
3 Naib Z M Nahmias A J Josey W E & Kramer J H Genital herpetic infection Association with cervical dysplasia and carcinoma Cancer *23* 94? 1969
4 Naib Z M Nahmias A J Josey W E & Zaki S A Relation of cytohistopathology of genital herpesvirus infection to cervical anaplasia Cancer Research *33* 1452 1973
5 Rawls W E Tompkins W A F & Melnick J L The association of herpes virus type 2 and carcinoma of the uterine cervix Am J Epidemiol *89* 547 1969

Submitted for publication February 21 1979

E Rubinstein M D
Department of Pathology
University of Uppsala
Box 553
S 751 22 Uppsala
Sweden

Acta Obstet Gynecol Scand 58 511–512 1979

ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1981

Date	Place	Name	Office
1980			
January 25–26	Linköping Sweden	XXI Meeting of the Nordic Association for Fertility and Andrology	Prof B Kjessler Dept OB/GYN University Hospital Linköping Sweden
February 10–16	Melbourne Australia	6th International Congress of Endocrinology	Congr Secr G P O Box 661 E Melbourne Victoria 3001 Australia
February 15–22	Jerusalem Tel Aviv Israel	International Congress on Gynecologic Endoscopy and Microsurgery	American Association of Gynecologic Laparoscopists 11239 South Lake Boulevard Downey CA 90241 USA
February 17–22	Monte Carlo Monaco	Seminar on Reproductive Medicine	Symposia Medicus 2815 Mitchell Drive Suite 116 Walnut Creek CA 94598 USA
March 18–22	Houston Texas USA	36th Annual Meeting of The American Fertility Society	The American Fertility Society 1608 13th Av South–Suite 101 Birmingham Al 35205 USA
March 21	London England	Symposium on Neonatal Care in Developing Countries	Inst of OB/GYN Queen Charlotte s Maternity Hospital Goldhawk Road London W 6 England
March 24–25	Chicago Illinois	International Symposium on Uterine and Placental Blood Flow	Susan A Shekelle Section Head Preventive Cardiology Chicago Heart Association 20 North Wacker Drive Chicago Ill 60606 USA
April 1–3	Atlanta Georgia	International Symposium on Pelvic Inflammatory Disease (PID)	Symp Director Ctr for Disease Control Building 1 Rm 3070 Atlanta Georgia 30333 USA
April 14–25	Baltimore *Maryland*	21st Postgraduate Institute for Pathologists *in Clinical Cytopathology*	John K Frost M D 601 Pathol Bldg The John Hopkins Hospital Baltimore Md 21205 USA
May 5–8	New Orleans LA USA	Annual Meeting of The American College of Obstetricians & Gynecologists	Warren H Pearse M D 1 E Wacker Dr Chicago Ill 60601 USA
May 21	London England	Symposium on Tubal Infertility	Inst OB/GYN *Queen Charlotte s* Maternity Hospital Goldhawk Road London W6 OXG England
May 6–28	Viareggio Italy	International Symposium on the Menopause Endocrinological & Pathophysiological Aspects	Serono Symposia Via Ravenna 8 I–00161 Rome Italy
May 27–31	*Hamburg* Germany	*International* Congress on Senology	Prof Dr H J Frischbier Universitäts Frauenklinik Martinistr 52 D 2000 Hamburg Germany
June 9–12	Gothenburg Sweden	XXI Congress of The Nordic Association for Obstetrics and Gynecology	Dr Hans Bergström Dept OB/GYN Sahlgrenska Hospital S–41345 Gothenburg Sweden
June 9–12	Ostend Belgium	Third International Congress on the Menopause	Int Menopause Society 8 Av Don Bosco B–1150 Brussels Belgium
June 16–20	Florence Italy	XI International Congress of the International Society of Psychoneuroendocrinology	Fondazione Giovanni Lorenzini Via *Monte Napoleone 23* I–20121 Milan Italy
June July 30–2	L Aquila Italy	International Symposium on Oligozoospermia	G Frajese Clin Med V–Policlinico Umberto I I–00100 Roma Italy

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1981

Continuation

Date	Place	Name	Office
1980			
July 3–5	*Bordeaux* France	*International Symposium on IUD Technology*	*Dr Karl Gösta Nygren University* Hospital S–75014 Uppsala Sweden
July 5–11	Madrid Spain	World Congress on Fertility and Sterility	Congr Secr Calle San Bernardo 5 Madrid 13 Spain
July 8–11	Edinburgh England	22nd British Congress of Obstetrics and Gynaecology	Royal College of Obstetricians & Gynaecologists 27 Sussex Place Regent s Park London NW1 4RG England
September 2–6	Berlin Germany	6th International Congress of Psychosomatic Obstetrics and Gynecology	Ass Prof Dr M Stauber Frauenklinik Charlottenburg der FUB Pulsstrasse 4 A–1000 Berlin 19 West Germany
September 4–7	*Kiwah Island* Charleston SC	*International Symposium on Carcinoma* of the Cervix Biology Etiology & Diagnosis	*E S E Hafez M D OB/GYN Wayne* State University Medical Res Bldg 550 E Canfield Detroit MI 48 01 USA
September 29–30	Freiburg Germany	International Congress on Endocrinology of Human Infertility	C Ferrari M D P O Box 995 Milan Italy
1981			
January 26–31	Mexico City Mexico	Pan American Congress of Andrology	Gerald Bagazinski Congr Admin 31600 West Chicago Livonia *MI 48150* USA

Acta Obstet Gynecol Scand 58 513–518 1979

SPONTANEOUS LABOR AND ELECTIVE INDUCTION — A PROSPECTIVE RANDOMIZED STUDY

I Effects on mother and fetus

John Tylleskär Orvar Finnström Ingemar Leijon Staffan Hedenskog and Gunnar Ryden

From the Department of Obstetrics and Gynecology Central Hospital Motala and the Departments of Obstetrics and Pediatrics University Hospital Linköping Sweden

Abstract In a prospective randomized study spontaneous and oxytocin induced labor for convenience have been compared with respect to uterine activity duration of labor the condition of the fetus and the newborn infant The study consists of 84 normal patients of whom 43 were induced at full term by amniotomy and oxytocin infusion using the Cardiff Infusion System Mark II 41 patients served as controls No difference in maternal age number of previous pregnancies and pelvic score one week before the day of delivery were found between the groups The following parameters were calculated duration of labor uterine activity amount of bleeding in the third stage of labor number of early and late decelerations as well as number of episodes of bradycardia in the CTG recordings birth weight Apgar score one and five minutes post delivery and blood gases in mother and child 60 seconds after delivery No significant differences between the two groups were found It is concluded that there are no increased risks to mother or fetus compared to normal labor provided that there is cephalic presentation and normal pregnancy careful selection with respect to the length of pregnancy and the condition of the cervix and that the Cardiff infusion system is used with intrauterine pressure recording and continuous fetal heart monitoring

The risk of complications in mother and fetus after elective induction compared to spontaneous labor is still a subject of debate (7 8 13 19 21) The disparate opinions can be partly explained by the selection of the patients in different studies and the difficulties in getting a comparable control group In recent years the development of equipment for continuous intrauterine pressure recording and fetal heart rate monitoring has made it possible to study the labor activity and the condition of the fetus during labor in more detail

We have compared the risks of elective induction with spontaneous labor in a prospective randomized study with special reference to the condition of the fetus and the newborn infant This paper will deal mainly with mother and fetus In other papers the neurological state of the newborn during the neonatal period (17) and the incidence of hyperbilirubinemia (18) have been investigated

In 1968 Turnbull and Anderson (24) described a method for induction of labor in which the infusion rate of oxytocin increased stepwise until a frequency of one contraction every third minute with a duration of at least 40 seconds was obtained This method has been developed further to the Cardiff Infusion System (12) The apparatus is constructed in such a way that the infusion rate of oxytocin is automatically and continuously increased until contractions with adequate strength and frequency are obtained This method for induction of labor gives standardized conditions and this system was therefore chosen for labor induction in the present study

MATERIAL

The study was performed in two clinics (Linköping and Motala) The investigation was approved by the Ethical Committee of the University of Linköping The group studied was selected from patients who fulfilled the following criteria

1 Maternal age 18–30 years for primipara and 18–35 years for multipara
2 Regular menstrual periods before the pregnancy The last menstrual period normal and the date known Patients using hormonal contraceptives had had at least three normal periods after completing the last course
3 Normal symphysis fundus distance and weight gain according to gravidogram (26)
4 Previous pregnancies and deliveries normal Birth weight 3 000–4 000 grams
5 Actual pregnancy normal and head presentation
6 Normal pelvic outlet on clinical examination

Patients who fulfilled these criteria were examined within one week before the expected date of delivery The condition of the cervix was judged on a ten point scale according to Westin (Table I) a modification of Bishop (3)

Table I *Pelvic scoring (0–10) according to Bishop modified by Westin*

Score	0	1	2
Dilatation	<0 5 cm	≥0 5 – 1 5 cm	>1 5 cm
Effacement	no	≤50 per cent	>50 per cent
Station	presenting part over the pelvic inlet	presenting part engaged at pelvic inlet	presenting part at spine or below
Consistency	firm	medium	soft
Position	posterior	middle	anterior

Primipara with a pelvic score of at least 5 points and engaged head and multipara with a pelvic score of at least 4 points were allowed to participate in the study If the patients accepted the constraints of the study they were divided randomly into two groups one group (I) in whom labor was induced on the expected day of delivery (± two days) and a second group (II) in whom delivery had to start spontaneously If the labor activity started earlier than the day of planned delivery the patients were excluded from the study If the pregnancy lasted more than 14 days beyond the estimated time of delivery labor was induced using intravenous oxytocin infusion This occurred in three patients who however were included in the spontaneous group

112 patient fulfilled these criteria and accepted the conditions of the study In 12 patients in the spontaneous group and 13 patients in the induced group the labor started before the day of planned delivery These patients were excluded from the study Three further patients were excluded One multipara in group II delivered so rapidly that recording during delivery and blood samples from the umbilical cord were not possible Two primipara one in each group were [illegible]ered by cesarean section because of feto-pelvic dis[illegible]ion and were also excluded Thus the total number [illegible]ts was 84 41 in the spontaneous group and 43 in [illegible]ed group The distribution the age of the patients [illegible]e pelvic score at the last antenatal visit are shown in [illegible]able II The number of previous pregnancies among multipara was the same in the induced group (1 5±0 7) and in the spontaneous group (1 3±0 6)

METHODS

Induction of labor (group I) After amniotomy an open ended saline filled catheter was inserted for measurement of the intraamniotic pressure and a scalp electrode was applied on the fetal head for continuous recording of the fetal heart rate using Hewlett Packard or Corometrics equipment Oxytocin was infused intravenously using the Cardiff Infusion System Mark II (4) The infusion was started 15 minutes after amniotomy The initial infusion rate was 1 mU/min and was increased continuously until the intensity of the contractions was at least 35 mm Hg and had a frequency of at least one contraction every 150 second The infusion rate of oxytocin doubled every 12 5 minutes

Spontaneous labor (group II) The patients were asked to come to the delivery ward as soon as labor started External CTG recordings were made until definite labor activity could be demonstrated i e uterine contractions with a frequency of at least one contraction every 5 minutes Amniotomy was performed an intrauterine catheter and a scalp electrode applied when in primipara the cervix was at least 50 per cent effaced and dilated more than 2 cm and for multipara when the cervix was dilated to at least 3 cm. Thereafter the recordings were made in the same manner as in group I

The dilatation of the cervix and the position of the head in the pelvis was recorded every hour and noted on a partogram

The day after delivery all mothers were required to answer a questionnaire about their experience of the induction

Obstetric analgesia In order to standardize the condition of the study as much as possible only the following methods of obstetric analgesia were used together with psychoprophylaxis according to Lamaze (16)

Nitrous oxide/oxygen 50/50

Pethidine chloride (Pethidine[R]) Hydroxizin chloride (Atarax[R]) 50 mg/50 mg

Pudendal block with 20 ml 0 5 per cent Mepivacaine chloride (Carbocain[R])

Analysis of the CTG-curve The uterine contractions were analyzed for a 30 minutes period at 6 cm dilatation of the cervix and the activity calculated in Montevideo units according to Caldeyro-Barcia *et al* (5)

The changes in heart rate pattern were judged according to Fisher (11)

Procedures at delivery Immediately after delivery the newborn infant was placed on the bed at the same level as

Table II *The patients studied age and the pelvic score at the last antenatal visit (mean value±SD)*

	Induction group (I)			Spontaneous group (II)		
	n	Mean age	Pelvic score	n	Mean age	Pelvic score
Primiparae	20	23 0 ±4 3	5 6 ±0 8	18	23 6 ±3 4	5 8 ±0 8
Multiparae	23	26 3 ±4 0	5 7 ±1 1	23	25 3 ±3 2	5 7 ±1 0
Totally	43			41		

Table III *The duration of labor in minutes from amniotomy (group I) from regular contractions (group II) and for both groups from a cervical dilatation of 4 cm (mean value±SD)*

	Induction group (I)		Spontaneous group (II)	
	Amniotomy	Cervix 4 cm dilated	Regular contractions	Cervix 4 cm dilated
Primiparae	353±141	222±109	485±203	317±208
Multiparae	.42±107	167±117	315±148	156±94

the vulva Exactly 60 seconds after delivery a blood sample from the umbilical vein and from an arterialized maternal finger tip were taken for pH and blood gas analysis After that 0 2 mg methyl ergometrine (Methergine[R]) was given intravenously to the mother The newborn was evaluated using the Apgar score after one and five minutes

Statistical methods Conventional statistical methods were used Student s t test was used to compare mean values

RESULTS

The duration of labor in the two groups is shown in Table III For the induction group the start of labor was calculated from amniotomy and for the spontaneous group from regular contractions with an interval of one contraction every 10 minutes The duration of labor was somewhat shorter in the induction group, the difference is however not statistically significant In the spontaneous group however the start of labor can be difficult to determine We therefore also calculated the duration of labor from the time when the cervix was 4 cm dilated As shown in Table III the duration of labor was slightly shorter in the induction group The difference is however not statistically significant

The uterine activity at 6 cm cervical dilatation was calculated In nine patients the intrauterine pressure was not recorded because of rapid labor and late arrival at the delivery ward The results are shown in Table IV The uterine activity was somewhat stronger in the induced group The difference was not statistically significant

The total amount of oxytocin used was 5 64±6 20 U for primipara and 4 40±3 20 U for multipara

Fetal heart rate patterns were analysed with respect to the occurrence of early and late decelerations as well as bradycardia Since marked changes in the fetal heart rate pattern are found just before delivery (15) the changes during the last 30 and 60 minutes are described separately The results are shown in Table V The only statistical difference observed between the groups was a significant increase ($p<0.05$) in the number of late decelerations during the last 30 minutes before delivery in the spontaneous group of primipara compared to the induced group

No statistical difference in the amount of bleeding during the third stage of labor was found between the groups (Table VI)

Three patients were delivered by vacuum extraction in the spontaneous group one with fetal distress and one with uterine inertia and in the induction group one patient had fetal distress One infant in the induced group was delivered in the occipito-posterior position otherwise all deliveries were in the occipito-anterior position

Placental retention occurred in one patient in each group

The condition of the newborn at delivery is summarized in Table VII No differences between the groups were found Nor were there any differences in maternal pH at delivery

Analgesia in the form of pudendal block or nitrous oxide was given in the same frequency in the two groups Pethidine/Atarax was however given more often to multipara in the induction group (87 per cent) compared to the spontaneous group (43 per cent) This difference is explained by the fact that

Table IV *Uterine activity at 6 cm cervical dilatation expressed in Montevideo units (mean value±SD)*

	Induction group (I)		Spontaneous group (II)	
	n	Montevideo units	n	Montevideo units
Primiparae	20	182±58	15	152±51
Multiparae	23	168±50	14	125±41

Table V *The number of early and late decelerations and the number of episodes of bradycardia in the CTG recordings (mean value±SD/30 min)*

	Primiparae			Multiparae	
	Minutes before delivery	Spontaneous labor	Induced labor	Spontaneous labor	Induced labor
Early decelerations	<30 min	3 4±2 3	2 7±2 1	2 4±2 9	2 1±1 9
	30−60 min	1 7±2 5	1 4±1 6	0 4±0 9	0 5±1 0
	>60 min	0 3±0 6	0 1±0 2	0 3±1 1	0 1±0 2
Late decelerations	<30 min	1 9±2 3	0 8±1 1	1 2±1 2	0 9±1 2
	30−60 min	0 7±2 3	0 2±0 4	0 0±0 2	0
	>60 min	0 1±0 2	0 0±0 1	0	0
Bradycardia	<30 min	0 2±0 4	0 4±0 5	0 3±0 7	0 2±0 4
	30−60 min	0	0	0	0
	>60 min	0	0	0	0

many multiparae in the spontaneous group arrived late in labor

An analysis of the questionnaire with respect to the patients experiences of the delivery indicate a positive attitude Thus 67 patients had a feeling of security with the electronic supervision of the uterine contractions and the fetal heart rate Only 10 patient felt uncomfortable No statistical differences between the groups were found Even though the analgesia given in the present study was restricted 58 per cent of the patients considered the analgesia to be sufficient

DISCUSSION

tion of labor for medical indications using am omy and intravenous oxytocin administration is generally accepted Disparate opinions concerning the risk for mother and child with elective induction of labor are found in the literature (7 8 13 19 21) This can be explained by the difficulties in obtaining a control group comparable to the group in whom induction of labor is performed to different techniques of oxytocin administration and the dose range of oxytocin used. The present prospective study was randomized and there was no differences in maternal age pelvic score or parity between the groups

Table VI *The amount of bleeding in ml during the third stage of labor (mean value±SD)*

	Induction group (I)	Spontaneous group (II)
Primiparae	376±216	339±242
Multiparae	326±267	243±106

The intraamniotic pressure was measured co tinuously and the oxytocin dosage was increased un the labor activity was at least 35 mm Hg and had frequency of at least one contraction every 150 s cond In this way effective labor was obtained Car ful selection of patients with a suitable pelvic sco ensured that all inductions were sucessful in the pr sent study The failure rate in previous studies vari from 0 4 per cent (2 9) to 12 5 per cent (14)

In spite of the rather rapid increase in the oxytoc dosage the duration of labor and the uterine activi measured in Montevideo units did not differ signifi cantly from the spontaneous group The materna obstetrical complications were few No differenc was found between the groups The material is how ever too small to permit a definite conclusion in th respect

Most arguments against elective induction for non medical indications have been directed towards in creased risk for the fetus during the delivery and th neonatal period Thus Favier and Helffreich (10 found that an increased basal tone in the uterus (>2 mm Hg) can cause deterioration of the acid bas

Table VII *Birth weight Apgar score and pH of um bilical venous blood 60 seconds after delivery (mea value±SD)*

	Induction group (I)	Spontaneous group (II)
Birth weight (g)	3 638±453	3 770±499
Apgar score 1 min	8 8±0 7	9 0±0 4
Apgar score 5 min	9 9±0 4	9 9±0 3
B-pH	7 35±0 07	7 33±0 07

balance of the child Toeff *et al* (23) found no direct correlation between the dose of oxytocin given and the incidence of hypertonus These results stress the importance of measuring the intraamniotic pressure and indicate the value of the Cardiff apparatus used which switches off the oxytocin infusion if the intra amniotic pressure exceeds 25 mm Hg for more than 120 seconds or 80 mm Hg for more than 10 seconds

Schwarcz *et al* (22) described an increased occur rence of type I Dips after elective induction compared to normal labor Their patient material was not ran domized and the number of previous deliveries and the use of analgesia during labor was not comparable between the groups The results are therefore difficult to interpret In the present study however no differ ence in early decelerations was observed

Amniotomy *per se* may increase the incidence of type I Dips according to Caldeyro-Barcia *et al* (6) In a well controlled study by Aladjem and Miller (1) ear ly artificial rupture of the membranes did not increase the incidence of early decelerations significantly Martell et al (20) observed a lower umbilical cord pH in newborns in whom early artificial rupture of the membranes was performed compared to the group with late rupture of the membranes However both groups had pH values within the normal range In the present study no difference in pH was observed within the induction and spontaneous group and the pH values were actually higher than those observed by Martell As will be discussed elsewhere (17) there were no differerences between the groups with regard to the neurological state during the newborn period The results concerning the condition of the fetus dur ing labor and at delivery obtained in the present study are similar to those found by Weaver *et al* (25) in 10 patients induced in the same way as in the present study It can be concluded that under the following conditions head presentation and normal pregnancy careful selection of patients with respect to the length of pregnancy and the condition of the cervix induc tion of labor using the Cardiff Infusion System with intrauterine pressure recordings and continuous fetal heart rate monitoring no increased risks for the mother and fetus occur during labor and delivery

REFERENCES

1 Aladjem S & Miller T Effects of spontaneous and artificial m mbrane rupture in labor upon fetal heart rate Brit J Obstet Gynecol *84* 44 1977

2 Alderman B Factors influencing planned delivery Clinics in Obstetrics and Gynecology *2* 19 1975

3 Bishop E H Pelvic scoring for elective induction Obstet Gynecol *24* 266 1964

4 Butterworths M J Automated incremental oxytocin infusion in the induction of labor Obstet Gynecol *44* 238 1974

5 Caldeyro-Barcia R & Poseiro J J Oxytocin and con tractility of the pregnant human uterus Ann NY Acad Sci *75* 813 1958

6 Caldeyro-Barcia R Schwarcz R L & Althabe O Effects of rupture of membrane on fetal heart rate pat tern Int J Gynaec Obstet *10* 169 1972

7 Chalmers I Lawson J G & Turnbull A C Evalua tion of different approaches to obstetric care Part II Brit J Obstet Gynaecol *83* 930 1976

8 Cole R A & Howie P W Elective induction of labor Lancet *1* 767 1975

9 D Esopo D A Moore D B & Lenzi E Elective induction of labor Am J Obstet Gynecol *89* 561 1964

10 Favier J & Helfferich M The effects on the fetus of an abnormal contraction pattern in the induction of labor with oxytocin Am J Obstet Gynecol *112* 1107 1972

11 Fischer W M Analyse und Beurteilung des Kardio-tokogramms *In* Kardiotokographie (ed Wolfgang M Fischer) pp 142 227 Georg Thieme Verlag Stuttgart 1976

12 Francis J G Turnbull A C & Thomas F F Automatic oxytocin infusion equipment for induction of labour J Obstet Gynaec Brit Comm *77* 594 1970

13 Hillemans H -G Mross F Schneller H & Steiner H Die programmierte Geburt Geburtshilfe Frauen heilkd *37* 373 1977

14 Howie P W & Mac Vicar J A comparison of the ef fect of administration of dilute oxytocin with oxytocin titration following amniotomy J Obstet Gynaec Brit Comm *77* 813 1970

15 Klöck F K Lamberti G & Sticherling C Die kind liche Herzaktion in der späten Eröffnungsperiode und in der Austreibungsperiode unter Berücksichtigung der klinischen Geburtsdiagnose *In* Archiv für Gynäkologie 211 band (ed H A Hirsch C Kaufmann & K G Ober) pp 272 Verlag von J F Bergmann München 1971

16 Lamaze F Qu est-ce que l accouchement sans doleur par la méthode psychoprophylactique Ses principes sa realisation ses résultats Paris Savour et Connaitre 1956

17 Leijon I Finnström O Hedenskog S Rydén G & Tylleskär J Spontaneous labour and elective induc tion a prospective randomized study Behavioral as sessment and neurological examination in the newborn period Acta Paediatr Scand *68* 553 1979

18 Leijon I Finnström O Hedenskog S Rydén G & Tylleskär J Spontaneous labour and elective induc tion a prospective randomized study II Bilirubin levels in the neonatal period Acta Obstet Gynecol Scand In press

19 Liston W A & Campell A J Dangers of oxytocin induced labour to foetuses Brit Med J *3* 606 1974

20 Martell M Belizan J M Nieto F & Schwarcz R

Blood acid base balance at birth in neonates from labors with early and late rupture of membranes J Pediatr *89* 963 1976
21 Martius G Terminierung der Entbindung und perinatale Sterblichkeit Erfahrungen mit 1875 programmierten Geburten Dtsch Med Wochenschr *101* 489 1976
22 Schwarcz R L Belizan J M Cifuentes J R Cuadro J C Marques M B & Caldeyro-Barcia R *Fetal and maternal monitoring in spontaneous labors* and in elective inductions Am J Obstet Gynecol *120* 356 1974
23 Toeff M E Hezroni J & Toeff R Induction of labour by pharmacological and physiological doses of intravenous oxytocin Brit J Obstet Gynaecol *85* 101 1978
24 Turnbull A C & Anderson A B M Uterine contractility and oxytocin sensitivity during human pregnancy in relation to the onset of labour J Obstet Gynaec Brit Comm *75* 278 1968
25 Weaver J B Pearson J P & Turnbull A C The effect upon the foetus of an oxytocin infusion in the abscence of uterine hypertonus J Obstet Gynaec Comm *81* 297 1974
26 Westin B Gravidogram and fetal growth Acta Obstet Gynecol Scand *56* 273 1977

Submitted for publication November 21 1978

J Tylleskär M D
Department of Obstetrics and Gynecology
Central Hospital
S 591 00 Motala
Sweden

Acta Obstet Gynecol Scand 58 519–526 1979

FETAL SYSTOLIC TIME INTERVALS IN LATE PREGNANCY EFFECT OF ATROPINE

Helge Jenssen

From the Department of Obstetrics and Gynecology Aker hospital Oslo Norway

Abstract Fetal systolic time intervals (FSTI) were derived from the externally recorded electrocardiogram and phonocardiogram in 74 women during late pregnancy The FSTI of the first 43 patients were recorded as a control In the others FSTI were registered before and after intravenous injection of atropine to the mother to increase the range of fetal heart rate Two patients in the atropine group were excluded

Correlation was found between the duration of the heart cycle (R R interval) and the mechanical systole (S_1 S_2 interval) before and after atropine

The amplitude of the initial part of the first heart sound (S_1) increased after atropine when postatropine tachycardia evidenced significant placental transfer of the drug

After atropine some fetuses showed initial bradycardia or bradycardia without following tachycardia In such periods of bradycardia S_1 amplitude was reduced

During the initial period of postatropine tachycardia short periods of constant R R interval combined with varying S_1 amplitude and S_1 S_2 interval occurred A close correlation was then present between S_{1a} amplitude and S_1 S_2 interval

The time from electrical to mechanical start of ventricular systole was measured as the R S_1 interval it did not vary with heart rate in the control group or in the atropine group before atropine was given Atropine shortened the R S_1 interval no correlation was found between shortening and tachycardia

It is concluded that in the fetus changes of FSTI can be observed from the externally recorded electrocardiogram and phonocardiogram Signs of peripheral circulatory change after atropine were not found

The changes observed after atropinization can be explained as a reduction of vagal tonic inhibition of cardiac chronotropism and inotropism Atropine also may cause a decrease of mitral valve flow

During pregnancy and labor fetal systolic time intervals (FSTI) have been shown to react to circulatory changes In severe erythroblastosis fetalis, shortening of the mechanical systole has been described (25) In the fetal lamb hypoxia shortens the preejection period (PEP) (23) In a case of fetal ectopic beats recorded during labor FSTI changes occurred changes related to uterine contraction also were found (11)

In newborn and children the mechanical systol[e] varies with heart rate while PEP seems to b[e] unrelated to heart rate (4 7)

The present investigation was planned to study th[e] relationship between FSTI and heart rate in th[e] human fetus

METHODS

FSTI were derived from the fetal electrocardiogram (FECG and fetal phonocardiogram (FPCG) recorded simultaneously on a modified Mingograph 34 (Elema Schönander Stockholm) paper speed 100 millimeter per second (mm/s) Considerable but unsuccessful efforts were made to record aortic valve opening (22) to measure PEP Instead the R S_1 interval and S_1 amplitude were measured The FPCG was recorded and read as described before (11) S_1 was composed of two parts denoted S_1 and S_{1b} (Fig 5 and Fig 6) A third component of the first heart sound described by Luisada in adults (17) could not be separated Fetuses with cardiac murmurs were not included

For external FECG recording the maternal skin was shaved scrubbed with sandpaper washed with diethyl ether and covered with electrode paste Circular Ag AgCl electrodes of 4 cm diameter were taped to the maternal skin at the symphysis pubis and at the uterine fundus where the fetal buttock could best be felt A reference electrode was taped proximally to the medial aspect of the mother s left thigh The signal was fed to a 50 Hz rejection preamplifier EMT 17 (Elema Schönander Stockholm) passed through a universal amplifier EMT 12 (Elema Schönander Stockholm) and to a final amplifier The time constant was 0 03-0 006 s gain set to 100-20μV The quality of the FECG should at least equal group V in the classification of Larks & Larks (15)

By adjusting the Mingograph ink jet to maximal curve sharpness at 100 mm/s and using a magnifying lens fitted to a desk lamp (Luxo 1001 Jac Jacobsen Oslo) reading to the nearest 2 5 milliseconds (ms) was possible each reading being the mean of 3 5 individual readings Parts of the curves with a relatively constant heart rate were chosen for analysis In the atropine group results are given before atropine and every second minute (min) afterwards The first postatropine reading was taken 2 min after the end of injection

Differences were compared statistically using standard error of the difference or Wilcoxon s signed rank test or two

Table I *Clinical details*

	Control group n=43		Atropine group n=29	
	Mean	Range	Mean	Range
Maternal age years†	25 4	17–33	26 2	17–39
Fetus				
Age of pregnancy at time of registration weeks	39 2	35–42	38 4	33–42
Days from registration to delivery	9 6	1–24	9 6	0–34
Newborn††				
Weight g	3 473	2 200–4 590	3 302	2 200–4 350
Apgar score 1 minute	8 4	4–9	8 6	4–9
Apgar score 5 minute	9 2	8–10	9 0	4–10
Placenta weight g	651	400–1 020	607	430–900

†Number of nulliparae in the control group 21 in the atropine group 15
††Number of boys/girls in the control group 19/24 in the atropine group 18/11
late clamping of the umbil cal cord

sample test (29) Correlations were computed on a Compucorp Statistician®

Patients Seventyfour patients with a single fetus in the vertex presentation were examined The pregnancies were judged to be normal from measurement of 24 hour urinary estriol excretion and placental cystine aminopeptidase and human chorionic somatomammotropine in maternal serum Amnioscopy and ultrasound cephalometry also were performed in most patients

The patients were studied in a calm atmosphere in the morning in the semisupine position with at least 20 left tilt to avoid the supine hypotensive syndrome

The FSTI of 43 fetuses were recorded and analyzed the results serving as a control Then the FSTI of 31 fetuses investigated before and after intravenous atropine the mother to accelerate the fetal heart rate (19) 1 mg + 0 1 mg per 10 kg body weight ‹red in 2 min the end of injection being taken as time The recorded parameters varied within almost the same limits in the control group and the atropine group before atropine (Table III)

In the atropine group ? patients were excluded one because of fetal movements with great variation of fetal heart rate the other because of technical breakdown after the atropine injection

Tachycardia after atropine was defined as an increase in fetal heart rate of at least 10 beats per min disregarding short time variation and reduction of the short time variation to less than 5 beats per min Twenty fetuses fulfilled the criteria and were called the atropine tachycardia (AT) group 9 fetuses did not develop tachycardia constituting the atropine non tachycardia (ANT) group

Table II *Maternal R–R interval before and 2 minutes after termination of intravenous atropine injection ms mean*

	Before atropine	After atropine
Atropine tachycardia group	706	451
Atropine nontachycardia group	684	453

RESULTS

Table I shows some clinical data There were 2 operative deliveries in the control group and 2 in the atropine group due to acute asphyxia during labor In the control group 11 and in the atropine group 1 patient was instrumentally delivered from other reasons (malpresentation cephalopelvic disproportion or secondary arrest of labor) One newborn in the atropine group scored Apgar 4 at 1 and 5 min of age but later did well In the control group one newborn whose mother had received pethidine 100 mg 2 hours before spontaneous delivery got Apgar score 4 at 1 and 8 at 5 min of age after Narcane (Endo Laboratories Inc) 0 1 mg given intravenously The other newborns behaved normally none showed signs of hematological or cardiovascular disease at two pediatric examinations during the 5 11 days hospital stay

R–R interval The maternal R–R interval (*Table II*) was a little shorter in the ANT group than in the AT group before atropine In both groups the maternal R–R interval shortened significantly showing adequate maternal atropinization

The fetal R–R interval varied between 350 and 513 ms (corresponding to fetal heart rate 171 117 beats per min) (Table III)

In the AT group tachycardia occurred on the average 6 min after injection the change of the R–R interval being statistically significant at this time

Table III *R–R S_1-S_2 and R–S_1 intervals in the fetus before atropine was given to the mother ms The atropine group is separated into tachycardia and nontachycardia groups*

	R–R interval			S_1-S_2 interval			R–S_1 interval		
	Mean	SE_{mean}	Range	Mean	SE_{mean}	Range	Mean	SE_{mean}	Range
Control group n=43	422	5 4	350–510	193	1 8	170–220	29 2	0 9	20–45
Atropine tachycardia group n=20	433	7 4	393–513	197	3	175–230	29 9	0 7	25–37 5
Atropine nontachycardia group n=9	423	13	355–500	187	5 3	160–207	30 8	1 8	25–42 5

Cardioacceleration continued during the next 8 min remaining unchanged during the rest of the experimental period

Twelve fetuses of the AT group showed initial bradycardia (Table IV) combined with a smaller R–R interval shortening than in the others of the group The difference in maximal tachycardia between the fetuses with and without initial bradycardia was statistically significant Also in the ANT group an initial period of bradycardia was found (Fig 1)

S_1-S_2 interval Before atropinization the means of the AT and ANT groups were not statistically different from the control group (Table III) In the AT group shortening of the S_1-S_2 interval occurred and was statistically significant 6 minutes after injection of atropine and during the rest of the experiment (Fig 2)

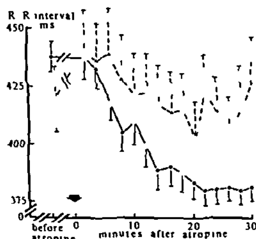


Fig 1 R–R interval of the atropine group ms milliseconds Mean ±1 SE_{mean} AT group ●—● ANT group ▲---▲ Arrow denotes end of atropine injection Plots are given every second minute

The trend of change resembled that of the R–R interval also regarding initial prolongation in the ANT group A close correlation was found between the S_1-S_2 and R–R intervals (Fig 3)

S_{1a} amplitude The mean values of the relative S_{1a} amplitude in the AT and ANT groups are shown in Fig 4 The S_{1a} amplitude increased after atropine in the AT group In the ANT group there was an initial reduction of S_{1a} amplitude corresponding to the initial bradycardia The 12 cases in the AT group with initial bradycardia showed a concomitant reduction of S_{1a} amplitude (Table V)

The S_{1a} amplitude in most cases was relatively low before atropine compared to the S_{1b} amplitude (Fig 5 A) but increased afterwards (Fig 5 B and C) The S_{1a} amplitude increase was not gradual but occurred at an accelerating rate

As the R–R interval shortening in the AT group started the normal beat to-beat variation of this interval diminished or disappeared in most cases In half of the cases in the AT group a close relationship between the S_1-S interval and S_{1a} amplitude could be shown to occur for a period of ½–4 min with constant R–R intervals (Fig 6) Later the S_{1a} ampli

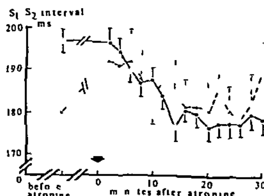


Fig 2 S_1-S_2 interval of the AT and ANT groups symbols as in Fig 1

Table IV *Fetal R – R interval in the atropine tachycardia group 8 patients without initial bradycardia compared to 12 with initial bradycardia ms*

	Before atropine		Maximal bradycardia		Maximal tachycardia		R – R interval decrease %
	Mean	SE_{mean}	Mean	SE_{mean}	Mean	SE_{mean}	Mean
No initial bradycardia n = 8	442	12			355	8	19 7
Initial bradycardia n = 12	432	8	466	9	381	6	11 8

Wilcoxon s two sample test (9) gives $p<0\ 01$ for the difference of maximal tachycardia between the cases with and without initial bradycardia

tude variation diminished Simultaneous changes of the duration of S_1 or S_2 were not observed This phenomenon was not seen in the cases with initial bradycardia where the beat to beat variation persisted

S_{1b} or S_2 amplitude did not change significantly

R – S_1 interval The mean duration before atropine is shown in Table III In the control group and atropine groups before atropine no correlation was found between the duration of the R – S_1 and R – R intervals (R – S_1 = 0 02 (R – R) + 38 9 r = 0 14) In the AT group no correlation was seen between the R – S_1 and R – R intervals when tachycardia and R – S_1 interval shortening were present

In the AT group the R – S_1 interval shortened significantly within 8 min (Fig 7) In the ANT group [illegible]ificant change occurred

[illegible] shortening started 3 – 26 min after atropine In [illegible] the R – S_1 interval shortened before tachycar[illegible] evident in 12 after this and in 4 cases the two changes set in simultaneously The R – S_1 interval shortening was not accompanied by broadening of S_1

DISCUSSION

When recording the R – S_1 interval instead of PEP the final part of the ventricular pressure rise time is lost S_1 starts shortly after mitral valve closure (17) The part of PEP lost seems to show the greatest reaction to various circulatory changes (8)

The S_1 amplitude is correlated to the rate of ventricular pressure rise (28) In adults it is the amplitude of the initial part of S_1 which changes but three parts of S_1 can be outlined (17) In the fetus only two divisions of S_1 could be delineated Only the first part showed varying amplitude The short R – S_1 interval in the fetus compared to adults makes it likely that the third part of S_1 seen in adults is lacking in the fetus Changes in fetal S_{1a} amplitude therefore give information about ventricular pressure rise changes

In adults the Q wave of the ECG is included when measuring the latent period from start of ventricular activation to start of the mechanical systole (Q – S_1 or Q – 1 interval) The Q wave of the FECG lasts 5 – 12 5 ms when measured from the scalp electrode FECG or the best external recordings where the Q wave was clearly visible The R – S_1 duration found agrees with a Q – S_1 duration of 35 ms reported in the fetus down to the age of 18 weeks (14) and 36 ms in the newborn (32) Measuring the R – S_1 interval externally and internally derived FECG may be compared

Comparing the intervals in the control group with those of the AT and ANT groups before atropine (Table III) it seems fairly unlikely that any systematic error has influenced the results Demarcation of the

Table V *The amplitude of S_{1a} in the atropine tachycardia group fetuses with initial bradycardia compared to those without mm*

	Before atropine			Maximal bradycardia			Maximal tachycardia		
	Mean	SE_{mean}	Range	Mean	SE_{mean}	Range	Mean	SE_{mean}	Range
No initial bradycardia n = 8	9 25	1	6 – 15				13 7	1 7	8 – 2[illegible]
Initial bradycardia n = 12	11 6	0 9	5 – 22	7 8	0 9	4 – 16	14 5†	1	8 – 21

Wilcoxon s signed rank test (*9) gives $p<0\ 01$ for the change

†Comparing the change from before atropine to maximal tachycardia with the same method gives $0\ 05>p>0\ 0$

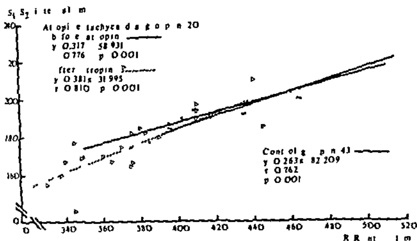


Fig 3 Relationship between the R – R and $S_1 - S_2$ interval in the control group and in the AT group before and after atropine Peeters & Bemmel's equation of correlation for normal cases $y = 0.32x + 54$ (25)

heart sounds especially S_1 as a rule improved after atropine

Duration of the $S_1 - S_2$ interval is as found by Peeters & Bemmel (25) in their normal cases and by Goodlin & Lowe (5) comparing their $Q - S_2$ minus $Q - S_1$ intervals with the present data The $S_1 - S$ interval is about 40 ms shorter than found by Walsh & Gyulai (32) in the newborn on the first day but not significantly different from their values on the 6th day postnatally Urbach *et al* (30) found a longer $S_1 - S_2$ interval in the newborn than in the fetus This may be caused by placentofetal transfusion of blood due to late clamping of the umbilical cord which was practised in the cases of Walsh & Gyulai (32)

The correlation between the R – R and $S_1 - S_2$ intervals is as reported in the fetus (25) newborn (32) and infants (7) However Goodlin & Lowe (5) did not find this relationship in the fetus

Atropine was applied to widen the range of fetal heart rate A relatively large dose was chosen as clinical routine has shown that it produces a better demarcation of fetal vagolysis than a smaller dose (10) but it does not induce maximal vagal block in all patients judged from the results of Chambarlain *et al* (2) in adults

The lack of response in the ANT group probably was caused by placental factors as maternal tachycardia was similar in the AT and ANT groups Fetal heart rate increased 14 1 per cent in the AT group In the sheep a fetal heart rate increase by atropine of 15 – 16 per cent was accompanied by complete block of acetylcholine response (31) Postmaturity may explain the lack of response in 3 fetuses of the ANT group (24) In another case estriol excretion became subnormal one week after the experiment in 2 other cases signs of mild preeclampsia developed within one week Delayed placental transfer of atropine may be found before other placental function tests show signs of deterioration Signs of placental transfer of atropine may be lacking even in normal pregnancies (10)

Small doses of atropine may induce bradycardia possibly as a direct cardiac effect (27) The initial bradycardia in the ANT group and in the fetuses of

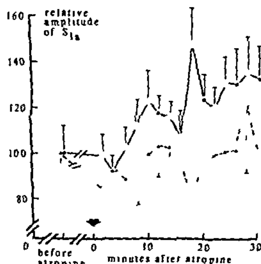


Fig 4 Relative amplitude of S_1 symbols as in Fig 1 The amplitude before atropine (in the AT group 10 25 mm in the ANT group 12 0 mm) set to 100 In the ANT group readings from 2 patients with low amplitudes are lacking at 28 minutes At 18 24 and 30 minutes the differences between the AT and ANT groups are significant statistically

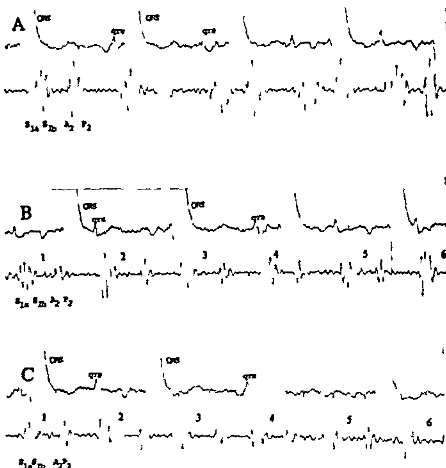


Fig 5 Kr Ho grav I 23 years 39 weeks amenorrhea QRS maternal ventricular complexes qrs fetal ventricular complexes S_{1a} and S_{1b} the two parts of S_1 A_2 and P_2 the two parts of S_2
A before atropine amplitude of S_{1a} is smaller than of S_{1b}
B 4 minutes after end of atropine injection in fetal cardiac cycles 2 and 6 the amplitude of S_{1a} is greater than of S_{1b} in cycles 3 and 4 the amplitude of S_{1a} is smaller than of S_{1b} In cycles 1 3 and 5 the amplitudes are about equal
C 7 minutes after atropine in 4 of the 6 cardiac cycles the *amplitude of S_1 is greater than that of S_{1b}*

T group showing relatively small heart rate in may be a sign of reduced atropine transfer
l precautions were taken to avoid peripheral g *in the mothers (20)* Symptoms of the supine ypotensive syndrome were not observed

Changes of the blood volume in the newborn during exchange transfusion markedly alter the duration of mechanical systole (6) Peripheral vascular pooling of blood in the fetus caused by atropine should shorten the S_1-S_2 interval However there is *no*

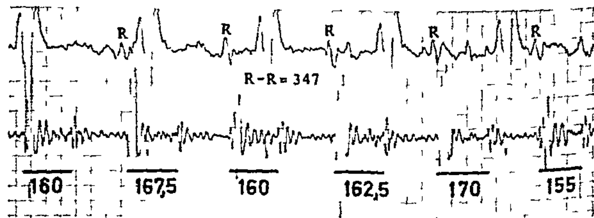


Fig 6 A K M *grav III para II 37 weeks amenorrhea Nine minutes after the end of atropine injection Duration of the R – R intervals is constant 347 milliseconds Duration of each S_1-S_2 interval given in milliseconds*

A direct correlation between the S_1-S_2 interval duration and S_1 *amplitude of each cardiac cycle can be seen The correlation equation of the next 30 heart cycles was* $S_1-S_2 = 0.33S_{1a} + 149.44$ $r = 0.78$ $p < 0.001$

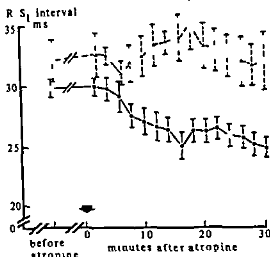


Fig 7 $R-S_1$ interval of AT and ANT groups symbols as in Fig 1

shift of the regression line describing the correlation between the $R-R$ and S_1-S_2 intervals after atropine (Fig 3)

The $R-S_1$ interval was not correlated to the weight of the newborn nor to the $R-R$ interval which is in contrast to the findings of Golde & Burstin (4) in infants and children Harris *et al* (7) found no correlation between isovolumetric contraction time and the $R-R$ interval In the present series a varying interval from registration to delivery (Table I) may have destroyed the correlation betweeen the $R-S_1$ and $R-R$ intervals

The effect of atropine on the $Q-S_1$ interval or PEP in adults i not clear both shortening (26) and prolongation (1) have been reported The post atropine $R-S_1$ interval was not correlated to the $R-R$ interval and in most patients did not shorten simultaneously with the onset of tachycardia Also the variation of the S_1-S_2 interval and S_{1a} amplitude at constant $R-R$ interval (Fig 6) makes it probable that atropine may have an inotropic influence on the fetal heart in addition to its chronotropic effect In adults the vagus nerves have been shown to exert a tonic inhibitory effect on ventricular inotropism (16)

Colebatch *et al* (3) cut the vagus nerve in fetal lambs and found reduced pulmonary flow When the peripheral cut end was stimulated pulmonary flow increased Thus atropinization should reduce pulmonary flow in the fetal lamb but Nuwayhid *et al* (21) could not confirm this

Acethylcholine constricts the human fetal ductus arteriosus (18) the effect is effectively blocked by atropine If the ductus arteriosus has a certain vagal tone atropine should cause dilatation Reduction of pulmonary flow and increased ductus flow decrease flow through the mitral valve In adults the $Q-S_1$ interval is correlated to mitral valve flow in right to left and left to right shunting (12 13)

The present investigation confirms the relationship between heart rate and mechanical systole found in the fetus (25) and in the newborn and children (7 32) The fetal heart alters its performance after atropinization the changes being measurable from the simultaneously recorded FECG and FPCG

The effect of atropine can be explained as inhibition of the vagal influence on cardiac chronotropism and inotropism Atropine also may change the central fetal circulation by altering pulmonary and ductus arteriosus flow The results speak against a peripheral vascular effect of atropine in the fetus when the drug is given via the mother in the doses applied here

REFERENCES

1 Auinger W Die QI Zeit und ihre Beziehungen zu links seitigen intrakardialen Druckkurven Wien Zeitschr Inn Med *47* 301 1966
2 Chamberlain D A Turner P & Sneddon J M Effects of atropine on heart rate in healthy man Lancet *II* 12 1967
3 Colebatch H J H Dawes G S Goodwin J W & Nadeau R A The nervous control of the circulation in the foetal and newly expanded lungs of the lamb J Physiol (Lond) *178* 544 1965
4 Golde D & Burstin L Systolic phases of the cardiac cycle in children Circulation *42* 1029 1970
5 Goodlin R G & Lowe E W Multiphasic fetal monitoring Am J Obstet Gynecol *119* 341 1974
6 Gyulai F & Walsh S Z Phonocardiographic studies during experimental hypo- and hypervolemia in the healthy newborn J Electrocardiol *4* 158 1971
7 Harris L C Weissler A M Manske A O Danford B H White G D & Hammill W A Duration of the phases of mechanical stystole in infants and children Am J Cardiol *14* 448 1964
8 Harris W S Systolic time intervals in the noninvasive assessment of left ventricular performance in man In Cardiac mechanics physiological clinical and mathematical considerations (eds I Mirsky D N Ghista and H Sandler) p 244 John Wiley & Sons Inc New York London Sidney Toronto 1974
9 Harris W S Schoenfeld C D & Weissler A M Effects of adrenergic receptor activation and blockade on

the systolic preejection period heart rate and arterial pressure in man J Clin Invest *46* 1704 1967
10 Hellman L M & Fillisti L P Analysis of the atropine test for placental transfer in gravidas with toxemia and diabetes Am J Obstet Gynecol *90* 1350 1964
11 Jenssen H Changes in fetal supraventricular extrasystoles during labour concentration Acta Obstet Gynecol Scand *57* 231 1978
12 Karnegis J N & Wang Y The Q-1 interval of the phonocardiogram in patients with ventricular septal defect patent ductus arteriosus and Blalock anastomosis Am J Cardiol *11* 452 1963
13 Karnegis J N & Wang Y Q-1 interval of the phonocardiogram in patients with atrial septal defect Br Heart J *28* 240 1966
14 Kelly J V The fetal heart Comparison of its electrical and mechanical events Am J Obstet Gynecol *91* 1133 1965
15 Larks S D & Larks Golda G Normal fetal electrocardiogram statistical data and representative wave forms Am J Obstet Gynecol *90* 1350 1964
16 Levy M N Ng M Lipman R I & Harrison Z Vagus nerves and baroreceptor control of ventricular performance Circ Res *18* 101 1966
17 Luisada A A The sounds of the normal heart p 48 Warren H Green Inc St Louis Missouri 1973
18 McMurphy Dorothy M & Boreus L O Studies on the pharmacology of the perfused human fetal ductus arteriosus Am J Obstet Gynecol *109* 937 1971
19 Mendez Bauer C Poseiro J J Arrellano-Hernandez G Zambrana M A & Caldeyro Barcia R Effects of atropine on the heart rate of the human fetus during labor Am J Obstet Gynecol *85* 1033 1963
20 Miller R D Kalser M H Frye Ch W & Gordon A S Measurement of atropine induced vascular pooling Circulation *10* 423 1954
…wayhid B Bronkman C R Su C Bevan J A & …h N S Development of autonomic control of …al circulation Am J Physiol *228* 337 1975
…Organ L W Bernstein A Rowe I H & Smith K C The pre-ejection period of the fetal heart Detection during labor with Doppler ultrasound Am J Obstet Gynecol *115* 369 1973
23 Organ L W Milligan J E Goodwin J W & Brain M J C The pre-ejection period of the fetal heart response to stress in the term fetal lamb Am J Obstet Gynecol *115* 377 1973
24 Pajntar M & Lavric M Atropine test and postmature pregnancy Obstet Gynecol (NY) *32* 520 1968
25 Peeters L A M & Bemmel J H van Fetal hypodynamic cardiac insufficiency in erythroblastosis fetalis Am J Obstet Gynecol *104* 883 1969
26 Raab W Paula e Silva Paulo de & Starcheska Yvonne K Adrenergic and cholinergic influences on the dynamic cycle of the normal human heart Cardiologia (Basel) *33* 350 1958
27 Rightmier D & Harwood B Atropine induced bradycardia Correspondence New Engl J Med *289* 1039 1973
28 Sakamoto T Kusukawa R MacCanon D M & Luisada A A Hemodynamic determinants of the amplitude of the first heart sound Circ Res *16* 45 1965
29 Steel R G D & Torrie J H Principles and procedures of statistics With special reference to the biological sciences pp 402-405 McGraw Hill Book Company Inc New York Toronto London 1960
30 Urbach J R Carrington E R Friel M A Rojas J F Zweizig H L Loveland M W Cavoto C M Tin M D & Lambert R L Characteristics of fetal heart sounds and murmurs in the second half of gestation Biol Neonat *13* 90 1968
31 Vapaavouri E K Shinebourne E A Williams R L Heymann M A & Rudolph A M Development of cardiovascular responses to autonomic blockade in intact fetal and neonatal lambs Biol Neonate *22* 177 1973
32 Walsh S Z & Gyulai F Electromechanical intervals in the healthy newborn J Electrocardiol *3* 259 19 0

Submitted for publication July 27 1978

Helge Jenssen M D
Department of Obstetrics and Gynecology
Aker Hospital
Oslo 5
Norway

Acta Obstet Gynecol Scand 58 527 – 530 1979

A NEW AND SENSITIVE METHOD FOR QUANTIFYING AND COMPARING THE BIOLOGICAL POTENCY OF VARIOUS ESTROGENS IN MAN

Mats Göran Damber Bo Sandström Bo von Schoultz and Torgny Stigbrand

From the Departments of Obstetrics and Gynecology and Physiological Chemistry University of Umeå Umeå Sweden

Abstract The serum level of an estrogen inducible plasma protein was followed by a radioimmunoassay in groups of women during treatment with various estrogens After an initial increase the mean value for the serum concentration was stable The plateau level after six months of treatment was taken as a parameter of estrogenic potency Eleven different hormonal preparations were compared and an estrogen index was constructed

Oral contraception and estrogen substitution around the menopause are rapidly becoming common as main indications for hormonal treatment A variety of estrogenic preparations are used in clinical practise Although they display many structural pharmacological and metabolic differences different substances are often used for the same indications Therapeutical side effects are mostly related to estrogenicity (11) and interest has focused especially on the differences between synthetic and so called natural estrogens (7 8 18) A lack of good methods for quantifying the estrogenic effect in the patient has precluded a comparison between different preparations and their side effects Estrogens like most steroids exert their biological effect by an altered m RNA pattern resulting in changed levels of both intra and extracellular proteins (9) Thus one way to quantify estrogenicity should be to follow such protein changes Estrogen treatment is known to cause elevated levels of several plasma proteins like transferrin α_1 antitrypsin thyroxine binding globulin and ceruloplasmin (1 10 16) Decreased levels have been reported for haptoglobin and orosomucoid (1 10 16) These changes during estrogen treatment are similar but not quite identical to those observed during pregnancy (16) The most pronounced increase has been reported for ceruloplasmin which during late pregnancy reaches about twice the initial non pregnant concentration (16)

The pregnancy zone protein (PZP) (13) by comparison is much more sensitive to estrogen stimulation Mean values are increased around fifty to one hundred times during late pregnancy i e from 10 – 20 to around 1 000 ug/ml (12) Also exogenous estrogen causes a marked rise in the serum concentration (4) Quantitative differences have been found between various preparations (4) The present study is an attempt to use this estrogen inducible plasma protein as an indicator of estrogenic potency

MATERIAL AND METHODS

A group of 37 apparently healthy women taking no other drugs were treated continuously with estrogen for climacteric disordes using the following scheme Twelve days 2 mg estradiol + 1 mg estriol ten days 2 mg estradiol + 1 mg estriol + 1 mg norethisterone and six days 1 mg estradiol + 0 5 mg estriol Venous blood samples were drawn for PZP determination before as well as after 4 8 and 12 months of treatment

A total of 174 women receiving treatment with various preparations for contraception or substitution around the menopause were investigated in the same way with venous blood samples before and after 6 months of treatment The allocation of the preparations and their contents are given in Table 1

The pregnancy zone protein (PZP) was measured by a radioimmunoassay (5)

RESULTS

The first group of women was followed during one year of treatment as seen in Fig 1 The mean value for the serum concentration of PZP before treatment was 77±7 6 ug/ml (mean ±SEM) After 4 months of treatment the mean had risen to 146 3±21 1 ug/ml an increase that was highly significant ($p < 0\ 001$) After this induction phase the mean level was very stable with no significant changes between 4 8 and

Table I *Composition of various estrogen preparations used for contraception or substitution in the menopause*

Code	Composition of drug	No of women
A	0 3 mg norethisterone	12
B	2 mg estradiol + 1 mg estriol	13
C	2 mg estradiol	9
D	2 mg estradiol vale ianate	9
E	2 mg estradiol + 1 mg estriol (12 days) 2 mg estradiol + 1 mg estriol + 1 mg norethisterone (10 days) 1 mg estradiol + 0 5 mg estriol (6 days)	16
F	4 mg estradiol + 2 mg estriol (12 days) 4 mg estradiol + 2 mg estriol + 1 mg noresthisterone (10 days) 1 mg estradiol + 0 5 mg estriol (6 days)	7
G	1 25 mg conjugated estrogen (mainly estrone sulphate and equilin sulphate)	31
H	4 mg estradiol + 2 mg estriol + 3 mg norethisterone	20
I	30 µg ethinyl estradiol + 0 15 mg levonorgestrel	10
J	50 µg ethinyl estradiol + 0 25 mg levonorgestrel	28
K	0 1 mg mestranol + 1 mg nor ethisterone	19

12 months the values for 8 and 12 months being al identical 129 8 and 127 0 ug/ml respectively the other groups of women therefore the level of PZP at six months was taken as a for estrogenic potency Fig 2 shows the relative increase of the mean value for PZP after hormonal treatment The increase was expressed in per cent of the initial mean value for the respective group before treatment Four preparations (A B C and D) did not cause a significant change while the remaining seven were found to significantly increase the PZP concentration For preparation A the only one without estrogen containing just 0 3 mg norethisterone there was a small decrease in concentration but this was not statistically significant Preparations E and F contained the same steroids (Table I) F containing twice the amount of E The expected E F ratio for PZP increase should therefore be 0 5 and the value determined from the actual plateau levels was 0 52 The same calculations could be made for preparations I and J with a theoretical value I J of 0 6 the observed value was 0 55 Thus the dose of estrogen was found to be related to the PZP level

There was no difference in the PZP increase between preparations B C and D which all contained 2 mg estradiol B also contained 1 mg estriol and no additional effect of this component was found 1 25 mg of conjugated estrogens (preparation G) gave roughly the same relative increase in PZP concentration as preparations F and H containing 4 mg of estradiol The three oral contraceptives containing ethinyl estradiol (I and J) and mestranol (K) gave a comparatively very high increase of PZP The mean value for the serum concentration after six months of treatment for the 19 women taking preparation K was 600 ug/ml corresponding to a relative increase of 1 375 per cent

DISCUSSION

After exogenous administration of estrogen the induction of PZP starts early and a plateau level is reached after 3 6 months of treatment The individual variation and the age dependent increase of this serum factor (6) made it necessary to express the effect of estrogen as the relative increase in the mean concentration of PZP within groups Six months of treatment was chosen to ensure stable plateau levels probably this time could be shortened

The induction patterns obtained with different preparations are in good agreement with clinical experience of their estrogenic potency Synthetic preparations such as ethinyl estradiol and mestranol were very high compared with so called natural estrogens In cases where a dose response comparison was possible the results were close to the theoretical estimate The values presented in Fig 2 might be

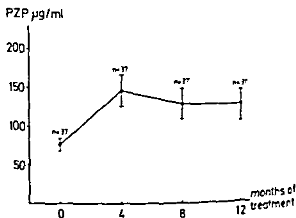


Fig 1 Mean values for the serum concentration of PZP (mean±SEM) in a group of women before and during one year of treatment with estrogen for substitution around the menopause

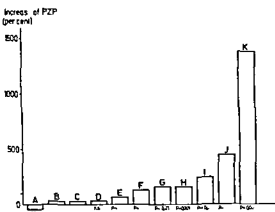


Fig 2 Estrogenic potency of various hormonal preparations for contraception or substitution around the menopause Values are expressed as the increase in per cent of the initial PZP mean value for each group before treatment The significance of the increase is given

taken to measure the total estrogenicity of different preparations used for contraception and pre and post menopausal substitution It is of interest that the highest induction level ever recorded in our laboratory (8 000 ug/ml) was found for diethylstilboestrol used for treatment of prostatic carcinoma (14) This value should be compared with 600 ug/ml obtained for preparation K in this study

The use of inducible plasma proteins as parameters for estrogenicity has several advantages Changes in concentration reflect the efferent expression of steroid influence Factors like intestinal absorption protein binding receptor affinity and intracellular metabolism are included in the net result of an increased protein synthesis Thus the estrogenic effect can be followed directly and quantified in patients sera

Among estrogen inducible proteins PZP is comparatively specific and the increase is very pronounced making this protein a sensitive parameter of exogenous estrogen The existence of cross reacting analogues also allows the use of animal models (15) The presented data allows the construction of a tentative estrogen index EI_{PZP} between increase of PZP and estrogen substance This index is readily calculated from the quotient between the relative increase in the concentration of PZP expressed in per cent of the mean for a group treated to reach the plateau level and the amount of estrogen substance in mg The mathematical expression is

$$EI_{PZP} = \frac{\%\ \text{PZP increase}}{\text{mg substance}}$$

To illustrate the possibilities of such an index some data drawn from the present material are given in Table II Assuming that estriol and norethisterone have no influence of their own the EI_{PZP}-values for micronized 17 β-estradiol irrespective of the preparation should be valid Preparations B and C both containing 2 mg of estradiol had a similar index in spite of the fact that preparation B also contained 1 mg of estriol This supports the assumption that estriol has no effect on PZP synthesis The values from preparations E F and H were somewhat higher which might suggest a weak additional estrogenic effect of the norethisterone in these preparations On the other hand 0 3 mg of norethisterone (preparation A) gave no increase of PZP perhaps higher doses of norethisterone are necessary to induce plasma protein changes in agreement with previous data (3)

The EI_{PZP}-values for the two synthetic substances ethinyl estradiol and mestranol were of quite another order around one hundred times higher The relation in estrogenic potency between conjugated estrogen and ethinyl estradiol has been suggested to be 1 100 (17) The corresponding figure from Table II is of the same order around 1 70 EI_{PZP}-values for ethinyl estradiol are based upon preparations I and J both containing levonorgestrel reported to have an antiestrogenic effect for example by reducing estrogen induced plasma protein changes (2) The presence of levonorgestrel and norehtisterone (K) could also explain the higher EI_{PZP} for mestranol than for ethinyl estradiol

The present EI_{PZP}-values derived from combined steroid preparations could be made more accurate by testing preparations containing only one active substance The values from such studies will describe the

Table II *Estrogen Index$_{PZP}$ for various steroids*

Substance	EI_{PZP}
Micronized 17 β-estradiol	18 (C)
Micronized 17 β-estradiol (in combination with estriol)	15 (B)
Micronized 17-β-estradiol (in combination with estriol and norethisterone)	34 (E) 33 (F) 41 (H)
Estradiol valerianate	0 (D)
Conjugated estrogens (mainly estrone sulphate)	130 (G)
Ethinyl estradiol (in combination with norgestrel	8 00 (I) 9000 (J)
Mestranol (in combination with norethisterone)	13750 (K)

Code of the preparatio accord g to Table I is g ven in parentheses

estrogenicity of the individual substances used in different pharmacological preparations Thus positive and negative effects of estrogen therapy could be compared on a dose activity basis

ACKNOWLEDGEMENTS

This study was supported by the Swedish Medical Research Council (4217) Tore Nilssons fund for Medical Research and Lions Research Foundation Umeå Skilful technical assistance was provided by Mrs A Andersson Mrs K Hjortsberg and Mrs M Wallen

REFERENCES

1 Briggs M H & Briggs M Effects of oral ethinylestradiol on serum proteins in normal women Contraception *3* 381 1971
2 Briggs M H & Briggs M Anti estrogenic effects of progestogens in normal women Life Sciences *11* 949 1972
3 Briggs M H & Briggs M Effects of some contraceptive steroids on serum proteins of women Biochemical Pharmacology *22* 2277 1973
4 Damber M G von Schoultz B Solheim F & Stigbrand T A quantitative study of the pregnancy zone protein in sera of women taking oral contraceptives Am J Obstet Gynecol *124* 789 1976
5 Damber M G von Schoultz B Stigbrand T & Carlström K A radioimmunoassay for the pregnancy zone protein Clin Chim Acta *66* 85 1976
6 Damber M-G von Schoultz B Stigbrand T Carlström K & Furuhjelm M Basic levels of the immunosuppressive serum protein PZ in women influence of age parity gonadotropins and estrogens Acta Obstet Gynecol Scand *56* 95 1977
Elkeles R S Hampton J R & Mitchell J R A Effect of oestrogens on human platelet behaviour Lancet *2* 315 1968
8 Gow S & MacGillivray J Metabolic hormonal and vascular changes after synthetic oestrogen therapy in oophorectomized women Brit Med J *2* 73 1971
9 King R J B & Mainwaring W I P Steroid cell interactions Butterworths London 1974
10 Laurell C B Kullander S & Thorell J Effect of administration of a combined estrogen progestin contraceptive on the level of individual plasma proteins Scand J Clin Lab Invest *21* 337 1968
11 Royal College of General Practitioners Oral Contraceptives and Health Pitman Medical London 1974
12 von Schoultz B A quantitative study of the pregnancy zone protein in the sera of pregnant and puerperal women Am J Obstet Gynecol *119* 792 1974
13 von Schoultz B & Stigbrand T Characterization of the pregnancy zone protein in relation to other α_2 globulins of pregnancy Biochim Biophys Acta *359* 303 1974
14 von Schoultz B Damber M G & Stigbrand T *In* Protides of Biological Fluids 24th Colloquium (ed H Peeters) p 189 Pergamon Press Oxford 1976
15 von Schoultz B Stigbrand T Martinsson K & Holmgren N Demonstration of analogues to the human pregnancy zone protein in animals Acta Endocrinol *81* 379 1976
16 Song C Merkatz J Rifkind A Gilette P & Kappas A The influence of pregnancy and oral contraceptive steroids on the concentration of plasma proteins Am J Obstet Gynecol *108* 227 1970
17 Speroff L Glass R H & Kase N G (eds) Clinical Gynecologic Endocrinology and Infertility The Williams and Wilkins Co Sec ed Baltimore 1978
18 Åstedt B & Jeppsson S 17β oestradiol and the fibrinolytic activity of vein walls J Obstet Gynecol Br Commonw *81* 719 1974

Submitted for publication March 30 1978

Bo von Schoultz M D
Department of Obstetrics and Gynecology
University of Umeå
S-901 85 Umeå
Sweden

Acta Obstet Gynecol Scand 58 531–533 1979

ENHANCEMENT OF THE AMYLASE CREATININE CLEARANCE RATIO IN PREGNANCY

R Naeije F Neuray A Van Melsen and A Delcourt

From the Departments of Internal Medicine Clinical Biology and Gynecology Ixelles Hospital Brussels Belgium

Abstract The renal clearance of amylase expressed as a proportion of simultaneous creatinine clearance (Cam/Ccr) was determined in 131 women in various stages of pregnancy No abnormal serum levels of amylase were found A moderate but significant increase in Cam/Ccr occurred during the last 15 weeks of pregnancy Possible causes for this change were investigated in smaller groups of subjects No increase in rapidly cleared isoamylase could be detected No modification in renal tubular handling of protein could be evidenced as assessed by measurements of the renal clearance of β_2 microglobulin expressed as a proportion of simultaneous creatinine clearance An increased glomerular permeability to amylase probably accounts for elevated Cam/Ccr in pregnancy

Pregnant women may present with nausea vomiting and epigastric distress When these symptoms are of sudden onset and accompanied by upper abdominal tenderness acute pancreatitis has to be suspected (2) However few studies on the effects of pregnancy on serum amylase activity are available and their conclusions are conflicting (1 3 4 6) Moreover while the renal clearance of amylase expressed as a proportion of simultaneous creatinine clearance (the amylase – creatinine clearance ratio Cam/Ccr) is actually used as a valuable index of pancreatic inflammation (12) no data are yet available on the behavior of amylase clearance during pregnancy

The present study shows that during pregnancy serum amylase remains low – normal and that Cam/Ccr may increase moderately both phenomenon probably due to pregnancy associated modifications in renal function

SUBJECTS AND METHODS

131 pregnant women aged from 16 to 37 years were studied None of them used drugs consumed excess of alcohol had a history of pancreatic gallstone liver or renal disease Those who presented complications of pregnancy were excluded Simultaneous blood and urine samples were taken from all the subjects for amylase and creatinine measurements Forty-eight healthy men and non pregnant women served as controls Serum and urinary isoamylase patterns were determined in 7 subjects at 6-15 weeks of pregnancy in 11 subjects at 6-15 weeks of pregnancy in 11 subjects at 16-30 weeks and in 7 subjects at 31-40 weeks Serum and urinary β_2 microglobulin were measured in 10 subjects at 6-15 weeks and in 10 subjects at 31-40 weeks

The amylase activity was determined by Van Loon s iodometric method (11) Creatinine was measured by an Autoanalyzer technique (Technicon) Cam/Ccr was calculated in a standard fashion (7) Renal tubular reabsorption of low molecular weight protein was evaluated by the measurement of the renal clearance of β_2 microglobulin expressed as a proportion of simultaneous creatinine clearance (the β_2 microglobulin-creatinine clearance ratio $C\beta_2/Ccr$) β_2 microglobulin levels were estimated by a radioimmunoassay using the Phadebas β_2 micro test (Pharmacia Laboratories)

The salivary (S type) and pancreatic (P type) isoamylases were separated by agarose gel electrophoresis and their concentrations measured with a chromogenic substrate (Phadebas) (10) Amylase S-type and P type isoenzyme clearances expressed as proportions of simultaneous creatinine clearances (CamS/Ccr and CamP/Ccr respectively) were calculated by the following formula (urine amylase × per cent isoamylase in urine × serum creatinine)/(serum amylase × per cent isoenzyme in the serum × urinary creatinine) × 100

The statistical calculations consisted of analysis of variance and Student s t test as indicated

Informed consent was obtained from all the subjects

RESULTS

The serum levels of amylase remained at the lower limit of normal throughout pregnancy (Table I) There was no tendency to decrease as judged by analysis of variance ($F=0\ 76$ $p>0\ 1$)

Cam/Ccr increased progressively from the 26th to the end of pregnancy (Table I) ($F-2\ 05$ $p>0\ 05$) This increase was moderate only 9 of the 74 women in the 26-40 week group presented values above 5 per cent considered as the upper limit of normal in our laboratory The highest observed value reached 6 5 per cent

Table I *Mean ±SEM values for serum amylase activity and Cam/Ccr at various stages of pregnancy and in normal controls Statistical comparisons are made between the successive groups of patients and the controls (Student s t test)*

Weeks of pregnancy	Number of subjects	Serum amylase (U/100 ml)	P	Cam/Ccr per cent	P
6–10	15	55±4	NS	2 8±0 2	NS
11–15	10	60±8	NS	2 4±0 3	NS
16–20	17	52±4	<0 01	2 7±0 2	NS
21–25	15	48±3	<0 005	2 9±0 3	NS
26–30	24	55±5	<0 05	3 2±0 3	<0 0?
31–35	22	54±4	<0 02	3 2±0 2	<0 005
36–40	28	52±3	<0 005	3 6±0 2	<0 001
Controls	48	66±3		2 4±0 2	

No significant variation in $C\beta_2$/Ccr was apparent when 2 groups of 10 subjects respectively in the first and in the last trimester of pregnancy were compared (Table II)

No significant variation in serum P type and S type isoamylase levels or in CamS/Ccr and CamP/Ccr was found when three groups of subjects respectively at *6-15 16-30 and 31-40 weeks of pregnancy were com*pared (Table III)

DISCUSSION

The behavior of serum amylase activity in pregnancy has been reported differently in previous studies Fitzgerald (4) described low serum amylase at the beginning of pregnancy rising steadily to reach the normal range at term Burt and McAlister (3) found serum amylase in pregnant women at term ?? Sominen and Karkonen (1) observed elevated serum amylase without information as to the stage of pregnancy Kaiser Berk and Fried handler (6) in the most recent and complete study reported a gradual rise in serum amylase until the 25th week and thereafter a slight fall 42 per cent of serum amylase values during the second trimester were above the upper limit of normal In the present work we found low normal serum amylase throughout pregnancy No explanation appears readily available for these discrepancies especially between Kaiser s findings and ours A saccharogenic technique was used in Kaiser s study to measure amylase activity while we used an iodometric method However the accuracy of both methods has been shown to be comparable for measurements of serum amylase activity (14) and the more time consuming saccharogenic technique has now been abandoned by most clinical laboratories

Cam/Ccr has been demonstrated to be a useful index of pancreatic inflammation (12) We observed a moderate but significant increase in Cam/Ccr during the last 15 weeks of pregnancy Several possible causative mechanisms have to be considered in the presence of an increased Cam/Ccr (13) The first a reduction in creatinine clearance is excluded in our subjects since pregnancy is known to be associated with a striking increase in the glomerular filtration rate (8) This accounts for the lowered serum creatinine levels in pregnant women (8) and probably also for the lowered serum amylase in our subjects The second a rise in P type isoamylase cleared more rapidly by the kidney than the other isoamylases is also excluded by our measurements The third is a modification in the renal transfer of amylase either at the level of the glomerulus or the tubule Many disorders in tubular function are associated with an increase in the urinary excretion of low molecular weight protein such as β_2 microglobulin (9) In acute pancreatitis Cam/Ccr and $C\beta$/Ccr both are elevated due to a modification in the tubular handling of amylase and other low molecular weight pro-

Table II *Mean±SEM values for $C\beta_2$/Ccr and for Cam/Ccr Two groups of patients respectively in the first and in the last trimester of pregnancy are compared (Student s t test)*

Weeks of pregnancy	No of subjects	$C\beta_2$/Ccr per cent	Cam/Ccr per cent
6–15	10	0 034±0 005	2 3±0 3
31–40	10	0 057±0 009	4±0 5
	P	NS	<0 01

Table III *Mean ±SEM values for serum P and S type isoamylase levels CamS/Ccr and CamP/Ccr in 3 groups of subjects Significance for variations is elevated by analysis of variance*

Weeks of pregnancy	No of subjects	Serum S-type isoamylase (U/100 ml)	Serum P type isoamylase (U/100 ml)	CamS/Ccr per cent	CamP/Ccr per cent
6–15	7	23±9	33±12	1 7±0 3	3 4±0 4
16–30	11	22±7	28±8	2±0 4	3 4±0 1
31–40	7	25±9	22±8	2 1±0 5	4 8±0 8
	F	0 31	1 53	0 3	0 2
	P	NS	NS	NS	NS

teins (5) Since in our subjects no significant variation in $C\beta_2$/Ccr was observed an increase in the glomerular permeability for amylase appears the most likely explanation for the increased Cam/Ccr in pregnancy

It has been suggested that during the second trimester of pregnancy the relative distribution of P type and S-type isoamylases would be altered with the S-type tending to dominate (6) Our data do not confirm this observation which was made on a small number of selected subjects Indeed in our subjects S-type isoamylase did not vary while P type isoamylase tended to decrease A larger number of measurements is needed however to evaluate the significance of this change

To conclude when acute pancreatitis is suspected in a pregnant woman the limits of normal and serum amylase activity as measured by Van Loon s iodometric method can safely be considered unaltered However a slightly higher upper limit of normal for Cam/Ccr has to be accepted in the last trimester of pregnancy

ACKNOWLEDGEMENTS

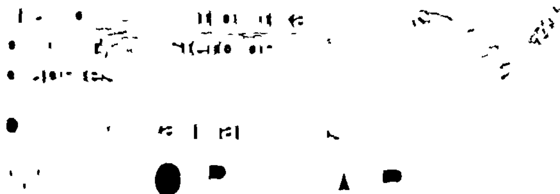
We thank Dr G Delespesse Service d Immunologie Transfusion Hôpital St Pierre 322 rue Haute B-1000 Brussels who performed the β microglobulin assays The secretarial help of Miss Ann Vanhaelewijck was greatly appreciated

REFERENCES

1 Adlercreutz H Soininen K & Karkonen M Oral contraceptives and serum amylase Brit Med J *3* 529 1972
2 Berk J E Smith B H & Akrawi M A Pregnancy pancreatitis Am J Gastroenterol *56* 216 1971
3 Burt R L & M Alister J A Serum amylase in pregnancy and in the puerperium and in the fetal blood Obstet Gynecol *28* 351 1966
4 Fitzgerald O Pancreatitis following pregnancy Brit Med J *1* 349 1955
5 Johnson S G Ellis C J & Levitt M D Mechanism of increased renal clearance of amylase/creatinine in acute pancreatitis N Engl J Med *295* 1214 1976
6 Kaiser R Berk J E & Friedhandler L Serum amylase changes during pregnancy Am J Obstet Gynecol *122* 283 1975
7 Levitt M D Rapoport M & Cooperband S R The renal clearance of amylase in renal insufficiency acute pancreatitis and macroamylasemia Ann Int Med *71* 919 1969
8 Lindheimer M D & Katz A I Renal changes during pregnancy their relevance to volume homeostasis Clin Obstet Gyn *2* 345 1975
9 Peterson P A Evrin P E & Berggård I Differentiation of glomerular tubular and normal proteinuria determinations of urinary excretion of β microglobulin albumin and total protein J Clin Invest *48* 1189 1969
10 Skude G Electrophoreti separation detection and variation of amylase isoenzymes Scand J Clin Lab Invest *35* 41 1975
11 Van Loon E J Likins M R & Seger A J A photometric method for blood analysis by use of starch iodine color Am J Clin Pathol *2* 1134 1952
12 Warshaw A L & Fuller A F Specificity of increased renal clearance of amylase in diagnosis of acute pancreatitis N Engl J Med *292* 325 1975
13 Warshaw A L The kidney and changes in amylase clearance Gastroenterology *71* 702 1976
14 Wettendorf P Schoenfeld P Adler M & Delcourt A Les amylases seriques et urinaires chez le sujet normal et en pathologie Arch franc Mal App Dig *63* 63 1974

Submitted for publication June 12 1978

R Naeije M D
Service de Medecine
Hopital Saint Pierre
322 rue Haute
B-1000 Brussels
Belgium



Acta Obstet Gynecol Scand 58 535–537 1979

NUCLEIC ACIDS AND PROTEIN CHANGES IN NORMAL AND PRE ECLAMPTIC PLACENTAE

Mohamed B Sammour Fawzia K Ibrahim Mohamed M A Fattah and Mohyi A Ramadan

From the Departments of Obstetrics and Biochemistry Faculties of Medicine and Science Ain Shams University Cairo Egypt

Abstract DNA and RNA assayed in the placentae of three groups of pregnant women normal second trimester (16-28) normal third trimester (28 weeks up to term) and in preeclampsia The protein level in the placentae of the three groups was also assayed

The proteins DNA and RNA all decreased after 28 weeks and up to term in normal pregnancy

In pre-eclampsia DNA and RNA showed a significant increase compared with cases of normal third trimester pregnancy Whereas the proteins also showed an increased level this was still less than its concentration during the second trimester of pregnancy

Protein/DNA and RNA/DNA ratios were calculated for the three groups These ratios showed a gradual decrease during normal pregnancy from 16 weeks up to term but with a sharper decrease in pre eclampsia

The total nucleotides of the pre-eclamptic placentae were reported to be significantly lower as compared with those of normal full time placentae (1) Ramadan et al (5) stated that the concentration of placental proteins were significantly increased in preeclamptic patients when compared with normal pregnant women

Weinberg (10) determined the relationship between gestational age and placental cellular replication using radioautography in placental specimens incubated in a culture medium of thymidin labelled tritium He supported the idea that early placental growth was hyperplastic

Winick (11) demonstrated that DNA synthesis or cell division normally ceases in human placentae around 34 to 36 weeks of gestation whereas the protein content continued to increase until shortly before term

Kobayashi Akihero (3) presented a correlation of nucleic acid and protein metabolism between the mother and the fetus during pregnancy and he concluded that RNA/DNA ratios increased in the fetal liver with the progress of gestation and decreased in the placenta Protein biosynthesis was therefore presumed to be high in the placenta

The present work was carried out to investigate the changes in the level of proteins deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) in the placenta during the second and third trimesters of normal pregnancy The same work was also carried on the placentae of pre-eclamptic patients A comparative analysis of both results may help to establish the functional activity of the placentae in pre-eclampsia where low birth weight infants are expected as a result of placental insufficiency

MATERIAL AND METHODS

Sixty pregnant women were selected from the Maternity Unit at Ain Shams University Hospitals in Cairo and classified into three groups

a) Twenty cases of normal mid trimester pregnancy with a gestation period ranging from 16-28 weeks

b) Twenty cases of normal third trimester pregnancy (from 28 weeks up to term) serving as a control group

c) Twenty cases of pre-eclampsia 10 of whom were considered to be mild and further 10 cases were severe

The duration of pregnancy ranged from 34-38 weeks The classification of the cases into mild or severe pre-eclampsia was based on the following criteria

1 The level of hypertension blood pressure above 140/90 but less than 160/100 mm Hg was labelled as mild case whil a blood pressure 160/100 or more was regarded as severe pre-eclampsia

2 Distribution of edema The case was considered mild pre-eclampsia if the edema was localised to the lowere limbs and the sacral area but if extending to the abdominal wall or if it was generalized edema the case was classed as severe pre eclampsia

3 Proteinuria if the proteinuria was less than one gm/1 000 ccs urine the case was mild pre-eclampsia while with heavier proteinuria the case was classed as severe pre eclampsia The deliveries of all instances were vaginal with no complications After draining as much blood as possible from the placenta a wedge was taken constituting the whole thickness of the placenta from its center to the periphery and promptly frozen at -20 C

Before the analysis the placenta was thawed washed several times with saline and 20 per cent by weight of the placental wedge was homogenized in water at 4 C The homogenate was then centrifuged at 3 000 r p m for 20

Table I *Description of 40 cases of normal pregnancy and 20 pre eclamptic patients submitted for nucleic acids and protein determinations*

No of cases	Type of cases	Age (years)	Parity
20	Normal pregnancy (16 – 28 weeks)	26 13±5 48	3 80±2 0
20	Normal pregnancy (28 weeks to term)	22 25±2 82	2 44±1 9
20	Pre-eclampsia	28 50±7 68	1 19±0 9

minutes at 4 C and the supernatent solution was made up to 10 mls volume in order to be used for analysis

Aliquots of one ml homogenate were used for quantitative assay of RNA and DNA by the method of Schneider (7) The optical density of the colour developed on using orcinol reagent in case of RNA was read at 660 mu whereas that obtained on using diphenylenediamine in case of DNA was read at 540 mu

Four samples were run in duplicate The concentrations of RNA and DNA equivalent to the optical densities were *obtained from comparison with standard curves Further* aliquots of homogenate were used for determining the total protein content using the method of Lowry Rosenbrough Farr and Randall as modified by Reider

RESULTS

1 The protein concentration in the placenta In the normal second trimester pregnancy (16-28 weeks) the protein concentration was the highest 2 995 gm/100 wet tissue as compared to normal third trimester ancy cases (28-40 weeks) where the protein to 2 160 g/100 g wet tissue

placental proteins in pre-eclamptic cases in ased to 2 33 g/100 g wet tissue (Table 2)

2 The ribonucleic acid (RNA) and desoxyribonucleic acid (DNA) of the placenta Both RNA and DNA were greatly increased in pre eclamptic cases compared with the two groups with normal pregnancy The figures for the second trimester normal pregnancy were higher than those for the normal third trimester pregnancy (Table 2)

The RNA and DNA concentrations showed statistically significant increase in pre eclamptic cases when compared to those of normal third trimester pregnancy

3 Protein/DNA ratio of the placenta This was calculated for the 3 groups normal second and third trimester pregnancy and pre eclampsia The corresponding ratios were 12 3 16 7 and 5 7 respectively On calculating the protein/DNA ratio for different cases it was found that these ratios decreased parallel to the concentration of the proteins which may indicate that the essential change in the placental nucleic acid contents is due to the DNA

DISCUSSION

In normal third trimester pregnancy the placental desoxyribonucleic acids (DNA) and ribonucleic acids (RNA) were greatly decreased when compared to their equivalents during the second trimester pregnancy In pre eclampsia they were significantly increased when compared to normal pregnancies these results were the opposite to what had been reported by Amma *et al* (1) but they agreed in some respect with the results obtained by Song Seung *et al* (9) DNA and RNA levels in pre eclamptic placentae were also higher than their concentrations in the placentae of normal pregnancy The protein concen

Table II *Concentration of RNA DNA and proteins in the placentae of 40 normal pregnancies and 20 cases of pre-eclampsia*

	16 – 28 weeks			28 – 40 weeks			Pre-eclampsia 34 – 38 weeks		
Parameters	Proteins† g/100 g	RNA	DNA	Proteins g/100 g	RNA	DNA	Proteins g/100 g	RNA	DNA
No of cases	20	20	20	20	20	20	20	20	20
Range	2 8 – 3 10	112 – 592	60 – 380	2 01 – 2 20	100 – 570	76 – 200	2 23 – 2 38	170 – 552	240 – 636
Mean	2 995	314 4	243 6	2 160	234	129	2 331	396	405
SD±	12 58	48 27	39 37	10 11	35 16	29 86	8 85	40 86	45 56
Significance p							<0 001		
Significance p								<0 001	
Protein/DNA		12 3			16 7			5 7	
RNA/DNA			1 29			1 81			0 98

RNA and DNA were expressed in this Table as mg/100 g fresh tissue

† Proteins was expressed as g/100 g fresh tissue

tration in the placentae was the highest during normal second trimester pregnancy then dropped near term In pre-eclampsia it showed a higher level than the cor responding figures for normal third trimester pregnancy but lower than the placental protein con centrations in the normal second trimester pregnan cy The RNA to DNA ratio showed a significant fall from the second to the third trimesters of normal pregnancy with a further fall in pre-eclamptic placen tae a situation which is parallel to that of protein to DNA ratio

The placental growth during pregnancy reaches its full maturity around 34-36 weeks Normally DNA synthesis or cell division ceases in the human placenta around 34 to 36 weeks of gestation but the protein content continues to increase until shortly before term (11) Our results support such statements in that the protein to DNA ratio increased from 12 3 during mid pregnancy to 16 7 near term

Killander (1966) Soensen (1957) and Zetterberg (1966) found that in the third trimester placenta significant steroid peptide and enzyme productions by the trophoblast were associated with increased ac cumulation of ribosomal RNA and proteins in the cytoplasm of the cells Our results of high RNA and protein contents in the placentae of pre eclampsia again support this finding Cellular RNA and protein content determined in trophoblastic cells in dependently should provide information on in dividual cell growth

It can be concluded that the rise of placental DNA in preeclampsia indicates a continuation of cell divi sion but such placentae show a low DNA/protein ratio indicating cellular hyperplasia but no hyper trophy and low functional activity of the cells

REFERENCES

1 Amma M K P Pathak R N & Deis P K Nucleic acid and nucleotides in toxemic placenta Ind J Biochem *6* 159 1969

2 Killander P Intercellular variability in normal and neoplastic populations in vitro A qualitative cytochemical study Almqvist & Wiksell Uppsala

3 Kobayashi A Correlation of nucleic acid and protein metabolism between mother and fetus during pregnan cy Nichidai Igaku Zaschi *28* 75 1969

4 Lowry O H Rosebrough N J Farr A L & Ran dall R R Protein measurement with folin phenol reagent J Biol Chem *193* 165 1951

5 Ramadan M A Sammour M B Ibrahim F K & Eisa E A Total proteins and amino acids of serum and placenta in normal and pre-eclamptic patients Int J Biochem *4* 29 1973

6 Reider H P Protein measurement in body fluids Clin Chim Acta *4* 733 1959

7 Schneider W P Extraction and estimation of deoxy pentose nucleic acid and of pentose nucleic acid J Biol Chem *161* 293 1945

8 Suensson G Exp Cell Res Suppl 4 165 1957

9 Song S & Kyu L Incorporation of tritium labelled uridine into RNA of the placenta and liver of mice in late half period of gestation Jae Hyn katollik Taehak Uihakpu Nonmunjip (Kouan) *24* 183 1973

10 Weinberg P C Cameron I L Parmely T Jeter R R & Pauerstein L Gestational age and placental cellular replication Obstet Gynecol *36* 692 1970

11 Winick M Brasel J A & Velasco E G Effect of prenatal nutrition upon pregnancy risk Clinical Obstetrics and Gynecology *16* 185 1973

12 Zetterberg A Nuclear and cytoplasmic growth during interphase Almqvist and Wiksell Uppsala

Submitted for publication July 10 1977

Mohammed B Sammour M D
Department of Obstetrics and Biochemistry
Faculty of Medicine and Science
Ain Shams University
Cairo
Egypt

Acta Obstet Gynecol Scand 58 539–542 1979

FERTILITY FOLLOWING LEGALLY INDUCED ABORTION

Erik B Obel

From the Department of Obstetrics and Gynecology YA University of Copenhagen Denmark and the Department of Gynecology Frederiksberg Hospital Copenhagen Denmark

Abstract The purpose of this study was to demonstrate if decreased fertility could be shown in women whose previous pregnancy had been terminated by a legally induced abortion

In 7 270 pregnant women fertility was measured as the time elapsed from the couple started sexual intercourse without using contraception to the present pregnancy This interval was called the latent period and fertility was defined as reduced if it was longer than one year

In women whose previous pregnancy had been terminated by legally induced abortion subsequent decreased fertility could not be shown when compared with women whose previous pregnancy had ended in a live birth the frequency of a latent period longer than one year not differing between these groups

When induced abortion had been complicated by pelvic inflammatory disease the frequency of a latent period more than one year was found to be higher than in women without this complication

To what extent the fertility of a woman may be decreased or destroyed because of damage to the reproductive organs caused by a legally induced abortion is not known The reason may be that a study dealing with this problem demands contact with the women several years after the procedure Such a contact might be embarrassing for the woman as the previous induced abortion may be concealed even from her nearest relations and in addition she may not want to be reminded of it So for ethical reasons such a personal contact would not be attempted in this country

In a study on pregnancy complications following legally induced abortion we have tried to evaluate if subsequent decreased fertility could be shown in this group of women

The study was based on the hypothesis that the damage caused by a legally induced abortion may be of varying degrees ranging from minimal damage in which case it is more difficult for the women to become pregnant to gross lesions likely to cause infertility The present study only dealt with the first problem and tried to evaluate whether decreased fertility could be shown after a previous legally induced abortion The fertility of a woman was measured as the time elapsed from the couple commenced sexual intercourse without using contraception to the woman became pregnant This interval called the latent period would be expected to be longer in women with a previous legally induced abortion if the procedure had caused such damage to the reproductive organs that fertility was impaired

MATERIAL AND METHODS

The study included all women 7 270 in all registered during the period 1st April 1974 to 31st December 1975 for delivery in two Copenhagen hospitals the Rigshospitalet and Frederiksberg Hospital All the women also participated in the WHO multicenter study Long term sequelae following legally induced abortion Obel (3 4 5) The study only included women with a regular menstrual pattern and an interval between menses of 21 35 days

At their first visit to the antenatal clinics all the women were interviewed by specially employed and trained staff

The latent period was recorded i e the time elapsed from the couple commenced unprotected sexual intercourse to the onset of last menstrual period before the actual pregnancy occurred If a woman became pregnant after delivery or an abortion without using contraception after the previous pregnancy the latent period was determined on the basis of first menstrual period followed by regular menses, with an interval of 21 35 days In cases where the woman became pregnant before first menstrual period after delivery or an abortion the woman was registered as pregnant in first cycle In women pregnant after they had stopped using the pill the latent period was registered in the same way on the basis of the first period followed by regular menstruation with an interval of 21 35 days In cases of oligomenorrhea after using the pill the latent period was registered on the basis of first menstrual period followed by regular menstruation with an interval of 21 35 days

Women who did not fulfil the definitions mentioned above women with ovulation induced by drugs and women treated with heterologous insemination were excluded from the study

A latent period more than one year was defined as decreased fertility

In addition the following descriptive variables were recorded in relation to the above mentioned WHO study age of the woman occupation education previous diseases including gynecological diseases previous pregnancies and

Table I *A latent period of more or less than one year in women whose previous pregnancy ended in a legally induced abortion a spontaneous abortion a live birth and in women with no previous pregnancies The Table also shows a latent period of more or less than one year in women whose previous pregnancy was terminated by legally induced abortion when the procedure was complicated by pelvic inflammatory disease in addition to those women without this complication*

Group	Result of previous pregnancy	No of previous pregnancies	Parity	No of women	Latent period ≤ 1 year No	Latent period ≤ 1 year per cent	Latent period > 1 year No	Latent period > 1 year per cent
1A	Legally induced abortion	1	0	277	233	84 1	44	15 9
2A	Spontaneous abortion	1	0	321	222	69 2	99	30 8[a]
1A	Legally induced abortion	1	0	217	182	83 9	35	16 1
3A	A live birth	1	1	213	173	81 2	40	18 8
1A	Legally induced abortion	1	0	277	233	84 1	44	15 9
4A	No previous pregnancies	0	0	279	211	75 6	68	24 4[b]
1M	Legally induced abortion	n	m	517	440	85 1	77	14 9
3M	A live birth	n	m	507	410	80 9	97	19 1
	Legally induced abortion (Complicated by pelvic inflammatory disease)	n	m	48	32	66 7	16	33 3
	Legally induced abortion (Not complicated by pelvic inflammatory disease)	n	m	469	408	87 0	61	13 0[a]

a = $p < 0.05$ (χ^2 test) b = $p < 0.05$ (McNemars test) $n \geq 1$ $m \geq 0$

their outcome delivery spontaneous abortion or induced abortion In those cases when the previous pregnancy was terminated by legally induced abortion the original abortion record was obtained On the basis of this record it was noted whether the procedure had been complicated by pelvic in tory disease

the first interview the data collected were entered form and the following four categories described

1 Women whose previous pregnancy was terminated by legally induced abortion (576 women)

Groups 2 Women whose previous pregnancy had ended in spontaneous abortion or still birth (1 009 women)

Group 3 Women whose previous pregnancy had ended in a live birth (2 900 women)

Group 4 Women with no previous pregnancies (2 755 women)

To study the latent period in women of group 1 with only one previous pregnancy called group 1A this group was compared with

Group 2A All women of group 2 with only one previous pregnancy ending in spontaneous abortion

Group 3A Women of group 3 with only one previous pregnancy (a pregnancy ending in a live birth)

Group 4A Women with no previous pregnancies

Group 3A and 4A were matched with group 1A using the matched pair technique described earlier Obel (4) The matching criteria used were age (5 year groups) and socio-economic status

Matching was made regardless of whether the latent period according to the definitions could be measured If the latent period could not be estimated the woman was afterwards deleted from the matched group This is the reason why the number of women in matched groups is not equal Only for 217 women of group 1A was it possible to find a control from among the women in group A

The total group 1 was also matched with women in group 3 the matched groups called group 1M and 3M respectively The matching criteria used were age (5 year groups) socio-economic status and parity Matching for parity was modified in such a way that women in group 1 with parity 0 were matched with women in group 3 with parity 1 For only 517 women in group 1 was it possible to find a control in group 3

STATISTICS

The frequency of a latent period of more than one year for matched groups was compared using the test described by McNemar (1) and 5 per cent was regarded as the significant level When the groups compared were not matched the marginal distributions were tested by χ^2-test and 5 per cent was regarded as significance level

RESULTS

The frequency of a latent period of more than one year did not differ between groups 1A and 3A nor groups 1M and 3M Table I and Fig 1 Table I shows a higher frequency of a latent period of more than one year in groups 2A and 4A when compared with group 1A

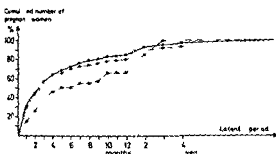


Fig 1 The latent period in women whose previous pregnancy had ended in a legally induced abortion Group 1M or in a live birth Group 3M The figure also shows the latent period in women in group 1M when the abortion was complicated by pelvic inflammatory disease
— Group 1M
-- Group 3M
Group 1M where the legally induced abortion was complicated by pelvic inflammatory disease

In women in group 1 where the induced abortion had been complicated by pelvic inflammatory disease the frequency of a latent period of more than one year was higher than in women without this complication Table I and Fig 1

It was further determined whether the groups compared differed as regards the descriptive variables which could be correlated with the latent period Only age was found to correlate with the latent period and it was also noted that there was a difference in ages between groups 1A and 2A

In all women studied the frequency of a latent period of more than one year before the age of 30 varied from 26 0-29 0 per cent Between 30 and 34 years the same frequency was 31 8 per cent and over the age of 34 years 41 2 per cent

6 1 per cent of the women in group 2A were over the age of 34 years and the equivalent figure in group 1A was 2 9 per cent This difference may to some extent be the cause of the higher frequency of a latent period of more than one year in group 2A when compared with group 1A

DISCUSSION

The purpose of this study was to show if decreased fertility could be demonstrated in women with a previous legally induced abortion The study only included women who had become pregnant and therefore the frequency of infertility could not be estimated The fertility of a woman was measured as the time elapsed from the couple started sexual intercourse without using contraception to the woman became pregnant This interval called the latent period was expected to be long in women with a previous legally induced abortion if the procedure had caused such damage to the reproductive organs that fertility was decreased

The study could not demonstrate an increased frequency of a latent period of more than one year in women whose last pregnancy had been terminated by legally induced abortion when compared with women whose previous pregnancy had ended in a live birth nor when compared with women pregnant for the first time nor with women whose previous pregnancy had ended in a spontaneous abortion The higher frequency of a latent period of more than one year after spontaneous abortion may as indicated be explained by the greater representation of women over 34 years in this group

The study also demonstrated an increased frequency of a latent period of more than one year in women whose previous induced abortion had been complicated by pelvic inflammatory disease when compared with women without this complication This may indicate that pelvic inflammatory disease following a legally induced abortion can lead to decreased fertility

Previous studies by Svanberg (7) and Kolstad (2) found that 5 1 per cent and 5 4 per cent respectively became infertile after legally induced abortion But these studies did not state clearly whether the infertility was due to the previous legally induced abortion

In a retrospective case-control study from Greece Trichopoulos *et al* (8) found a relative risk of infertility after induced abortion of 3 4 when comparing the frequency of induced abortion in women examined because of infertility with women admitted for delivery As the control group does not include women in whom that particular pregnancy had ended in a spontaneous abortion or an induced abortion the estimated risk may be too high especially if the frequency of previous induced abortion is higher in these two groups when compared with women admitted for delivery Induced abortion is not legalized in Greece and it is uncertain whether a history of induced abortion could be elicited with the same degree of accuracy in women admitted for delivery as in women examined for infertility If not the estimated risk of infertility may be too high

The latent period which in the present study is us-

ed as a measure of fertility may be influenced by many different factors in both partners concerned including the frequency of coitus Ryder & Westoff (6)

The aim of the present study was only to evaluate if legally induced abortion could reduce female fertility To minimize the influence of irregular ovulation upon the results the study only involved women with a regular menstrual pattern Matching for age was undertaken to make the groups comparable as age was found to be correlated with the latent period As there were too few women with a previous spontaneous abortion matching with this group was not done

We tried to obtain information concerning the frequency of coitus in order to determine if differences could be shown between the groups However for each woman this frequency differed greatly from week to week and it was impossible to obtain reliable retrospective information especially from those women with a long latent period For this reason we did not obtain any meaningful correlation between frequency of coitus and the latent period Nevertheless it seems reasonable to presume that matching for age decreased a possible difference in frequency of coitus between the groups

Information concerning the fertility of the partner was only available when the couple had been examined especially for infertility Therefore it was impossible to describe either the frequency or kind of de male fertility in the groups compared

CONCLUSION

Decreased fertility could not be demonstrated in women whose previous pregnancy was terminated by legally induced abortion when compared with women whose previous pregnancy had ended in a live birth or a spontaneous abortion or with women pregnant for the first time Only in women whose previous legally induced abortion had been complicated by pelvic inflammatory disease was there decreased subsequent fertility when compared with women without this complication

ACKNOWLEDGEMENTS

The study has received financial support from the Danish Medical Research Council

REFERENCES

1 Fleiss J L Statistical methods for rates and proportions Wiley Interscience New York London Sidney Toronto 1973
2 Kolstad P Therapeutic abortion Acta Obstet Gynecol Scand Suppl 6 1957
3 Obel E B Pregnancy complications following legally induced abortion Description of the study population with special reference to factors correlated to prematurity Dan Med Bul *26* 192 1979
4 Obel E B Pregnancy complications following legally induced abortion (To be published)
5 Obel E B Pregnancy complications following legally induced abortion with special reference to abortion technique Acta Obstet Gynecol Scand *58* 147 1979
6 Ryder N B & Westoff C F Reproduction in The United States 1965 Princeton University Press Princeton New Jersey 1971
7 Svanberg N Senkomplikationer vid legal abortprovokation Nord Med *42* 1264 1946
8 Trichoupoulos D Handanos N Danezis J Kalandidi A & Kalapothaki V Induced abortion and secundary infertility Br J Obstet Gynecol *83* 645 1976

Submitted for publication July 27 1978

Erik B Obel M D
Ved Højmosen 138
DK 2979 Hørsholm
Denmark

Acta Obstet Gynecol Scand 58 543–546 1979

HETEROGENEOUS RESPONSE OF DISSEMINATED HUMAN OVARIAN CANCERS TO CYTOSTATICS IN VITRO

C Trope K Aspegren S Kullander and B Åstedt

From the Tornblad Institute and the Department of Gynecology and Obstetrics Malmö General Hospital University of Lund Sweden

Abstract Cell suspensions from nine human ovarian primary cancers their metastases and ascitic cells were treated *in vitro* with amethopterin and melphalan Effects were measured by incorporation of H^3 TdR or H^3 UdR into the cells There was significant heterogeneity of cytostatic effects on cells from the three sources in a given patient Ascitic cells did not represent a mean of the cancer cell clones The implications of these findings should be considered if cytostatic *in vitro* prediction tests are used to guide cytostatic treatment of patients

An *in vitro* test system which can predict the sensitivity of malignant tumors to cytostatic drugs would be of great help in clinical practice Several such systems have been devised For review see Tanneberger (14) and for late references Mattern *et al* (7) and Volm *et al* (19) So far no system has been described with adequate *in vivo* *in vitro* correlation for human tumors although an attempted correlation has been reported by several authors (2 3 9 15 20 21) Fair correlation between *in vivo* and *in vitro* results have been reported in animal tumors (13 8 7) Using short term incubation of cells suspensions Håkansson and Trope (4) have shown that for methylcholantrene induced mouse sarcomas there exists a correlation between cytostatic drug effects *in vitro* and *in vivo* (16)

Using the same *in vitro* method the heterogeneity of response to cytostatic drugs of a single tumor was studied in the same animal system Different parts of a tumor differed significantly to cytostatic treatment *in vitro* (5) A similar heterogeneous response was found in human adenocarcinomas of the stomach and colon (17) but not in non Hodgkin lymphomas (18)

The present investigation was done in order to investigate whether metastasizing human ovarian cancers with ascites are heterogenous to cytostatic drugs in vitro and if the ascites cells are representative of the abdominal parent and daughter tumors and thus can be used for prediction of response to such drugs

MATERIAL AND METHODS

Nine patients with metastasizing ovarian cancer with non hemorrhagic ascites yielded the tumor material At exploratory laparotomy two to six pieces were taken from the primary tumor and its peritoneal metastases as well as a sample of ascitic fluid The solid tumor material was divided with scissors in Parker 199 culture medium (SBL Stockholm) and brought into a suspension of single cells or small tissue fragments by pressing through a fine stainless steel mesh Cells were obtained from ascitic fluid by low speed centrifugation Hemorrhagic ascitic fluid was not used The cells were then washed once in Parker 199 and finally resuspended in Parker 199 without protein additives and distributed to test tubes

The following cytostatic drugs were added to give the following final concentrations Melphalan 0 2 mg/ml (Alkeran Burroughs and Wellcome London) and amethopterin 0 05 mg/ml (Methotrexate Lederle Wayne) The solution of melphalan in Parker 199 was freshly prepared for each experiment The other drug was diluted from stock solutions The concentrations of cytostatic drugs were calculated according to experiments on normal thymocytes from mice The lowest concentrations which in these experiments gave an almost complete inhibition of H^3 thymidine incorporation were used All incubations were carried out in Parker 199 and were set up within 90 minutes after the operation

The tumor cells were incubated with melphalan for 3 hours Then H^3 thymidine (H^3 TdR methyl H^3 thymidine spec act 1 9 Ci/mM Schwartz/Mann Bio Research Inc Orangeburg) was added to give a final concentration of 2 μCi/ml and the incubation was continued for a further hour In experiments where the effect of amethopterin was tested the cells were preincubated for 1 hour before the addition of deoxyuridine 6-H^3 (H^3 UdR spec act 24 1 Ci/mM The Radiochemical Centre Amersham) to give a final concentration of 2 μCi/ml and the incubation was continued for a further 3 hours Controls were set up in each series of experiments to which only H^3 TdR or H^3 UdR respectively was added All tests were performed in duplicate Preparation of cells for determination of DNA and radioactivity has previously been described in detail (4) H^3 thymidine or H^3-deoxyuridine incorporation into DNA was determined with the aid of liquid scintillation The DNA content of each sample was determined DNA synthesis was expressed as precursor incorporation per DNA units (4)

In order to get near normally distributed variates suitable for statistical analysis and especially for variance analysis

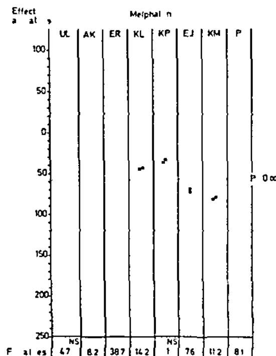


Fig 1 Effect of melphalan on H^3 TdR incorporation *in vitro* into primary tumors and solid metastases (solid squares) and into ascitic cells (crosses) from nine patients with ovarian cancer Effect values i e difference between control tubes and malphalan treated tubes are given in the graph The 0 1 per cent significance level is marked as a horizontal dashed line Variance ratios (F values) and their ficance levels estimating the variance between effects mary tumor solid metastases and ascitic cells from a are given at the bottom NS denotes not significant $p<0\ 05$ denotes $p<0\ 01$ and denotes .001

the following expression was used (12)

$$a = 100 \times \log_{10} \times \frac{cpm \times 10^4}{(AES) \times (DNA)}$$

where (cpm) is the number of counts registered (AES) is the cpm registered with automatic external standardization and (DNA) is the amount of DNA in the sample expressed in arbitrary units corrected for the standard curve The effect of cytostatic drugs is expressed as the difference between the mean a value in the two control tubes and the mean a value *in the two tubes where cells were tested with cytostatic* drugs

RESULTS

The nine tumors differed in histological malignancy However within a given tumor and its metastases no histological differences were found Among the tumor cells there may occur invading lymphocytes and macrophages The proportion of such cells in the cellsuspension from the primary tumor and its metastasis was very low and may not influence the DNA measuring The ascitic fluids from the different patients contained 20-30 per cent mesotheloid cells and/or lymphod cells leucocytes and fibroblasts Additional autoradiographic studies of these cells has shown a minute and negligible DNA synthesis The effects of the two drugs on the incorporation of H^3 TdR or H^3 UdR into tumor cells from different biopsies and from ascites cells are shown in Fig 1 and Fig 2 There are differences in sensitivity within some tumors To evaluate these differences an analysis of variance was performed to estimate the interaction between the two sources of variation biopsies and drug effect (5) The variance due to interaction between these two sources is compared with the general (technical) error variance i e variance between identically performed incubations

It is obvious that all tumors tested with amethopterin reacted similarly in so far that there was significant heterogeneity of response of the separate biopsy specimens including ascitic cells Moreover in all patients but one (ER) there are both sensitive and resistant biopsies when tested with amethopterin With melphalan two tumors (UL AK) showed a uniform response in all biopsies while the remaining six tumors responded heterogeneously In five tumors tested with melphalan there were both sensitive and *resistant biopsies* The ascitic cells differed in response from the biopsy specimens i e did not represent a mean of the entire tumor

DISCUSSION

The results show that there are differences in the response to cytostatic treatment *in vitro* between tumor biopsies from one patient with metastasizing ovarian cancer which thus contain cell lines with varying sensitivity towards such drugs This difference may be due to local nutritional factors resulting in variations in the proliferation rate Another explanation could be that these was a variation in the amount of necrotic tissue in the various biopsies and *in the* number of invading lymphocytes and macrophages Such variables should cause differences in the incorporation of H^3 TdR or H^3 UdR in the control tubes from different biopsies from a tumor However no such differences were found between control tubes in the present investigation Furthermore the influence of varying numbers of fibroblasts *mesothelial or* lymphatic cells is probably negligible as the additional autoradiographic experiment demonstrated their very

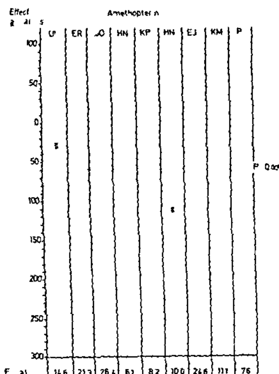


Fig 2 Effects of amethopterin on H^3 UdR incorporation on the same tumor cells as in Fig 1 For explanations see text to Fig 1

low DNA synthesis The observed differences between tumor fragments therefore are very likely to be due to other factors The presence of two or more clones of tumor cells differing in their sensitivity towards cytostatic drugs is a possbile explanation Cytogenetic and cytochemical studies have demonstrated such clones in experimental animal tumors (1 6 10 11) and in human cancer of the colon and stomach (17) The present work indicates that various clones may also exist in human ovarian cancers In contrast to these solid tumors lymphomas of non Hodgkin type are not heterogenous toward cytostatic *in vitro* (18)

Differences in heterogeneity might partly explain why cytostatic treatment of solid disseminated tumors of colon ovaries or stomach is often less sucessful than that of lymphomas

Several attempts have been made to develop *in vitro* tests which can predict the sensitivity of malignant tumors to cytostatic drugs Since the majority of such tests have been performed on tumors from human subjects the correlation of results *in vitro* and *in vivo* have been difficult to asses The best correlation has been with leukemias and non Hodgkin lymphomas probably because of the monoclonal character of these tumors For solid adenocarcinomas however no system has been devised which gives adequate correlation *in vitro* or *in vivo* A likely explanation of this fact is the demonstrated heterogeneity From the present study it is evident that ascitic cells are not representative of all the cell clones of the solid tumor and thus do not reflect a mean of the tumor To obtain representatives of most of the cell clones several biopsy specimens must be taken from the parent tumor as well as from its metastases

ACKNOWLEDGEMENT

The work was supported by grants from the Faculty of Medicine University of Lund Sweden and the John and Augusta Persson foundation

REFERENCES

1 Bishun N P Mills J Lloyd N & Williams D C Chromosomal examination of various cell clones (*in vitro*) derived from a DMBA (7 12 dimethyl alpha benzantracene)-induced male rat breast tumor Eur J Cancer *9* 865 1973
2 Bickis I J Henderson I W D & Quastel, J H Biochemical stud es of human tumors II *In vitro* estimation of individual tumor sensitivity to anticancer agents Cancer (Philad) *19* 103 1966
3 Cline M J & Rosenbaum E Prediction of *in vivo* cytotoxity of chemotherapeutic agents by their *in vitro* effect on leucocytes from patients with acute leukemia Cancer Res *28* 2516 1968
4 Håkansson L & Tropè C An *in vitro* study of the effect of cytostatic drugs on DNA synthesis in methylcholanthrene induces mouse sarcomas and in rat Walker 256 tumors Acta Path Microbiol Scand Sect A *81* 552 1973
5 Håkansson L & Trope C On the presence within tumors of clones that differ in sensitivity to cytostatic drugs Acta Path Microbiol Scand Sect A *82* 35 1974
6 Ito E & Moore G E Characteristic differences in clones isolated from an S_{37} ascites tumor *in vitro* Exp Cell Res *48* 440 1967
7 Mattern J Kaufmann M Volm M Schütze U Wayss K Goertler KI & Tasca C Zur Sensibilitätstestung maligner menschlicher Tumoren gegenüber Cytostatica II Klin Wschr *50* 196 1972
8 Matthias M Tanneberger St & Gummel H Vergleichende Untersuchungen klinisch aquivalenter Dosen verschiedener Zytostatika am Ehrlich Ascites Karzinom der Maus under Walker Karzinosarkom 256 der Ratte *in vivo* und in der Zellkultur (*in vitro*) Arch Geschwulstforsch *36* 240 1970

9 McDonald G O Stroud A N Brues A M & Cole W H *In vivo* and *in vitro* assay for drug effect on cancer cells Ann Surg *157* 785 1963
10 Mian N Cowen D M & Nutman C A Glycosidases heterogeneity among dimethylhydrazine induced rat colonic tumors Br J Cancer *30* 231 1974
11 Mitelman F The chromosomes of fifty primary Raus rat sarcomas Hereditas (Lund) 69 155 1971
12 Nordqvist S Hormonal responsiveness of human endometrial carcinoma studied *in vitro* and *in vivo* Thesis Lund Studentlitteratur 1969
13 Seidel H J & Wegner L A Zur Sensibilitätsbestimmung von Tumoren *in vitro* I Vergleichende Untersuchungen am Jensen Sarcom *in vivo* und bei 1 stündiger Inkubation *in vitro* Z Krebsforsch 72 105 1969
14 Tanneberger St Gewebekultur und Krebschemotherapie Arch Geschwulstforsch *31* 387 1968
15 Tanneberger St & Bacigalupo G Einige Erfahrungen mit der individuellen zytostatichen Behandlung maligner Tumoren nach prätherapeutischer Zytostatika Sensibilitätsprüfung *in vitro* (Onkobiogramm) Arch Geschwulsforsch *35* 44 1970
16 Trope C & Håkansson L An *in vitro* study of cytostatic drug effect on the DNA synthesis in methylcholantrene induced mouse sarcomas Correlation between *in vitro* results and the response *in vivo* Acta Path Microbiol Scand Sect A *8?* 189 1974
17 Trope C Håkansson L & Dencker H Heterogeneity of human adenocarcinomas of the colon and the stomach as regards sensitivity to cytostatic drugs Neoplasma *22* 423 1975
18 Björklund A Håkansson L Stenstam B Tropé C & Åkerman M On heterogeneity on non Hodgkin lymphomas as regards sensitivity to cytostatic drugs As *in vitro* study In press Eruop J Cancer 1980
19 Volm M Mattern J & Wayss K The effects of cytostatic drugs on transplanted tumours An investigation of the correlation between in vivo and in vitro results Arch Geschwultsforsch *43* 137 1974
20 Wolberg W H & Brown R R Autoradiographic studies of *in vitro* incorporation of uridine and thymidine by human tumor tissue Cancer Res *22* 1113 1962
21 Wright J C Medrek T J Walker D G & Lyons M M The current status of chemotherapy and hormone therapy for cancer Progr Clin Cancer *1* 264 1965

Submitted for publication July 5 1978

C Trope M D
Department of Obstetrics and Gynecology
Malmö General Hopsital
University of Lund
214 01 Malmö
Sweden

Acta Obstet Gynecol Scand 58 547–553 1979

DETERMINATION OF MYOMETRIAL TENSION DURING LABOR BY COMBINED MICROTRANSDUCER IUP RECORDING AND ULTRASONIC EXAMINATION OF THE UTERINE CAVITY

U Ulmsten K E Andersson K Lindström and P H Persson

From the Department of Obstetrics and Gynecology and Biomedical Engineering University Hospital Malmö Sweden and the Department of Clinical Pharmacology Institute of Pharmacology University of Århus Århus Denmark

Abstract In twelve women in whom labor was induced by oxytocin infusion intra uterine pressure (IUP) was recorded by micro-transducers and simultaneously the diameter of the uterine cavity was estimated by means of ultrasound Myometrial tension was calculated according to the law of Laplace In the ten women who were delivered within eight hours after the start of induction myometrial tension was clearly higher than in the two in whom induction failed No technical problems were encountered during the registrations which in some cases lasted for more than five hours It is suggested that with the described technique a more accurate determination of myometrial activity is possible than with the generally used methods for IUP recording The technique might facilitate evaluation of drug effects on the uterus during labor and improve the IUP part of intra partum clinical monitors

Accurate determination of myometrial tension during labor remains a great problem in obstetrics (1) Assuming that the pregnant uterus at term has a spherical shape myometrial tension can be calculated according to the law of Laplace if the intra uterine pressure (IUP) and the radius of the uterine cavity are recognized simultaneously With but few exceptions (8) IUP recording during labor has so far been performed with balloon catheters or open-end catheters with or without flow connected to conventional transducers Due to wellknown bio-technical disadvantages exact determination of IUP by these techniques especially during long time recordings *in vivo* may be complicated (14) Recently micro-transducers have been used for recording intraluminal pressures in the urinary tract (3) and this technique seems superior to previously used methods also for recording intra uterine pressure (19 20) In many obstetric departments ultrasonic examination of the uterus of pregnant women has been performed as a routine for several years By combining the micro-transducer technique for recording of the IUP and ultrasonic examination for determination of the radius of the uterine cavity it should be possible to calculate myometrial tension during labor This report gives our experiences with the combined investigation technique in women admitted for induction of labor

MATERIAL AND METHODS

Subjects Twelve pregnant women with uncomplicated pregnancy admitted at term to the obstetrical ward participated in the study Their mean age was 24 years (range 19-33 years) mean parity 0 7 (range 0-3) and mean gestational age 40 weeks (range 39-42 weeks) Before the investigation informed verbal consent was obtained In all subjects head presentation of the fetus existed No spontaneous uterine contractions were present The cervix was effaced and dilatation varied from 2 to 4 cm

Pressure recordings The intra uterine pressure (IUP) was recorded by means of a dacron catheter in which one or two micro-transducers were enclosed (Fig 1) The actual technique as well as its clinical application has been described in detail elsewhere (2 3 18 19 20)

Due to the construction of the recording equipment a zero pressure equal to the actual atmospheric pressure could be presented on the graph when requested Before and after the recordings the catheter was calibrated electrically and hydrodynamically (2) It should be emphasized that with the present recording equipment no fluid is necessary for the pressure measurement

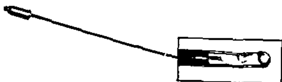


Fig 1 Micro-transducer catheter used for extra amniotic pressure recording



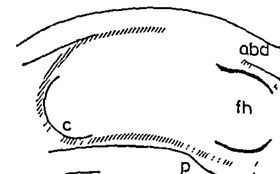


Fig 2 Ultrasound tomogram from one of the patients The polaroid photo is taken from the sagittal section in the mid line *The abdominal wall* (abd) and the promontorium (p) clearly visable The fetal head (fh) is seen in the pelvic The smallest radius (r_m) is calculated from the circle ..ich best corresponds to the most curved part of the uteri

In eight of the twelve women external tocography was performed simultaneously with IUP recordings using a tocodynamometer (Roche *Medical Instruments) The* signals from the tocodynamometer and the micro-transducer(s) were registered by the same recorder

Ultrasonor technique The ultrasound examination was performed with the subject *in the supine position using the* compound B scan technique (Kretz) or a multielement scanner (Philips) Two-dimensional polaroid films were taken of both the sagittal and the transversal cross section of the uterus in the mid line From the series of *polaroid pictures* the widest and smallest diameters of the uterus were determined (Fig 2) The smallest radius of the fundal uterine cavity was determined from pictures taken in the mid line

Experimental procedure As part of the routine at the department the women were examined with ultrasound prior to the present investigation in order to localize the placenta Women with low implanted placentas were excluded as *introduction of a recording catheter extra amniotically* in these subjects might involve a risk of damaging the placenta

The recording catheter was introduced transcervically into *the uterine cavity As a rule the micro-transducer was* placed 8 10 cm from the internal os In two women however it was initially placed only 2-4 cm from the internal os in order to record the pressure in the lower uterine segment at the initiation of labor In another two women a catheter with two micro-transducers was used The distal transducer was placed 6-8 cm and the proximal about 2-4 cm from the internal os The recording catheter was introduced by means of a nylon tube (Catheter Guide Roche Medical Instruments) routinely used at the *department for transcervical* introduction of conventional open-end IUP recording catheters The localization of the micro-transducer was estimated by measuring the length of the introduced catheter *and the shape of the uterine cavity as displayed on the* ultrasonor screen The position of the recording catheter was secured by attaching it to the inside of the thigh of the subject By an extension cable the catheter was connected *to the amplifier and the recorder Because of this arrangement* the woman could move relative freely during the recordings which could be performed in either the supine lateral or upright position The IUP recordings and the *ultrasound examination used for calculation of myometrial* tension (see below) were performed with the subjects in the supine position The uterine contractions were induced by intravenous infusion of oxytocin starting at a rate of 2 mU *per minute When labor had been established the ultrasonic* examination was repeated

Definitions and interpretation of the recordings The pregnant uterus has a complex form This impedes exact calculations of the myometrial tension and extensive *simplifications are required* to obtain a mathematical model which can be used for analogies An elementary structure which has many characteristics in common with a pregnant uterus is a thinwalled elastic tube (Fig 3)

To derive a relation between the pressure p in the tube and the resulting surface tension T consider Fig 3 The force F acting on a small element 2 Δ S of the surface is

$$F = 2\,\Delta S\,p \qquad (1)$$

If we study a part of the tube with the length l and consider the small surface area 2 Δ S equation (1) can be rewritten as

$$F = 2\,r\,\alpha\,p\,l \qquad (2)$$

From the force parallelogram the relation between force and surface tension is

$$F/2 = \alpha\,T \qquad (3)$$

Combining of equations (2) and (3) gives

$$2\,r\,\alpha\,p = 2\,\alpha\,T \qquad (4)$$

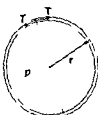
or

$$p = T/r \qquad (5)$$

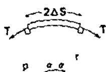
The pregnant uterus does not exactly correspond *to a thin walled tube The theory for the tube can however be* extended so that any small portion of a curved surface can be fitted to a surface shaped like a blow-out pat h i e having two different radii of curvature in mutually *perpendicular directions If these radii known as the principal* radii of curvature are called r_1 and r_2 the general expression for the pressure differential is

$$p = T\,(1/r_1 + 1/r_2) \qquad (6)$$

A thin walled sphere where the radii of curvature are equal in any two perpendicular directions and equal to the radius r of the sphere gives the relation

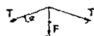


Thin-walled
ELASTIC TUBE



$F = 2\Delta S p$ (1)

$F = 2 r \alpha p$ (2)



$F/2 = \alpha T$ (3)

$(2)+(3) \Rightarrow$

$2 r \alpha p = 2 \alpha T$ (4)



$p = T/r$ (5)

$p = T(1/r_1 + 1/r_2)$ (6)

$p = 2T/r$ (7)

Fig 3 Calculation of myometrial tension

$$p = 2\ T/r \quad (7)$$

Considering the uterine cavity it might be difficult to measure the different radii involved As the *smallest radius* has the greatest influence on the pressure surface tension relation we used that radius for our calculations giving

$$p = 2\ T/r_{min}$$

or

$$T = \frac{1}{2}\ (p\ r_{min}) \quad (8)$$

where p = intra uterine pressure T = myometrial tension and r_{min} = smallest radius of the uterine cavity Selection of r_{min} was facilitated by attaching flexible plastic rings of different diameters to the ultrasonor screen An exact measure of r_m was then obtained from the polaroid films that were taken to confirm the ultrasonic findings (see Fig 2)

The *resting intra uterine pressure* (Fig 4) is defined as the lowest pressure (in mm Hg) between uterine contractions *Amplitude* or *intensity* of contractions is the difference between the peak pressure during a contraction and the resting pressure The *duration* of a contraction is the time in seconds from the point where the intra amniotic pressure has increased by 10% above the resting pressure to the point where the pressure has decreased to the same level *Frequency* of contractions is the number of contractions occurring in 10 minutes The *rise time* of the uterine contraction is defined as the time needed to increase the IUP from 10% to 90% of its maximum value

The calculations were based on data from 20 consecutive uterine contractions at a time when the patients had regular myometrial activity The recordings lasted between 90 and 300 minutes For detailed IUP analysis the normal paper speed was intermittently increased from 10-25 to 50-100 mm per second

RESULTS

As seen in Table I induction of labor was successful in ten of the investigated women who were delivered within 8 hours In these patients the mean frequency of contraction was 4 contractions per minute (range 3 5) The resting pressure averaged 13 mm Hg (range 8 20 mm Hg) and the amplitude 51 mm Hg (range 40-60 mm Hg) The duration was 76 seconds (range 70-84 seconds) and the rise time 3 4 mm Hg per second (range 2 2-4 6 mm Hg per second) The rise time increased with increasing intensity of the myometrial contraction It was observed that as soon as labor was established a moderate increase occurred in the intensity of the contractions

The ultrasonic examination was easily performed at the initiation of labor and could then be repeated intermittently Uterine wall thickness and the size of the uterine cavity including its smallest radius were estimated as described above Myometrial tension was then calculated and the results are given in Table I Uterine wall thickness showed small variations and was not used in these calculations As can be seen in Table I myometrial tension varied between 110 and 165 mm Hg per cm in the ten women in whom induction was successful In two subjects the induction of labor failed This means that despite increased infusion of oxytocin (up to 24 mU per minute) no effective labor was established and the cervical dilatation was almost unchanged When the infusion of oxytocin was stopped the uterine contractions ceased In these women myometrial tension was clearly lower than in those in whom induction was successful Further in the failures resting pressure and frequency were higher duration of contraction shorter and rise time lower than in the successful

IUP and external tocography In the eight women in whom simultaneous IUP recording and external tocography were performed it was found that the external tocography gave satisfactory recordings only for a short time after optimal adjustment When the women changed position the external recording often deteriorated

At the initiation of labor in the four subjects in whom IUP was recorded in the lower segment of the

Table I Numerical values of the recorded parameters

Patient	r p	F	I	D	r t	MT	c d
Successful induction							
G J	11	4	52	72	3 0	156	5
A M O	20	5	52	70	2 3	110	3
J R	10	3	43	74	2 3	113	3
R M J	8	4	55	79	3 9	110	5
M S	14	4	44	70	2 4	120	3
E J	12	4	52	78	3 0	130	4
I S	18	4	56	84	3 8	140	4
S M	10	3	61	79	4 6	153	5
A M S	18	5	60	76	4 5	165	5
L P	10	4	49	74	3 0	125	3
Mean	13	4	51	76	3 4	131	5
Range	8–20	3–5	40–61	59–84	2 2–4 6	110–165	3–5
Failure							
E N	23	6	41	53	2 1	93	3
G R	21	6	38	54	2 0	95	3

R p = intra uterine resting pressure mm Hg F = number of contractions/ten minutes I = Intensity of contraction mm Hg D duration of contraction seconds r t = rise time i e speed of contraction mm Hg/second MT = myometrial tension according to the law of Laplace T = A(p r) c d = cervical diameter cm (See also text)

uterus it was found that when uterine contractions occurred as judged from the simultaneously per formed external recording there was a fall in the uterine pressure in the lower segment (Fig 5) This decrease in pressure was most pronounced at the very initiation of labor When the head of the fetus engag pelvic inlet an increase in the pressure of the part of the uterus was found simultaneously the myometrial contractions (Fig 4) This was so the case shortly after puncture of the mem branes which was deliberately performed in two of the subjects (Fig 6)

The pressure recording technique functioned without any problems during all recordings The calibrations *before and after the investigations* were in complete accordance No accidental rupture of the membranes occurred when introducing the recording catheter or during the recordings The delivered children weighed more than 2 500 g and had 1 minute Apgar scores of 8 9

DISCUSSION

Recordings of IUP should be performed before rupture of the membranes because otherwise the laws of Laplace and Pascal are not applicable (5) For biophysical reasons intra amniotic pressure recordings are to be preferred to extra amniotic measurements In the present study no intraamniotic pressure recordings were performed It has however been found that extra amniotic IUP recordings before rupture of the membranes are in accordance with intra amniotic IUP measurements (5)

Previous investigators have demonstrated the technical problems with the IUP recording catheters such as clotting of the measuring aperture lack of exact zero pressure and leakage from micro-balloons It has been claimed that a more reliable standardized technique should lead to an improvement of the IUP recordings (5 14) So far the presented micro-transducer technique seems to fulfil these expectations since no technical problems were encountered during the investigations which sometimes lasted for more than 5 hours It should however be emphasized tha the micro-transducer technique does not solve all problems connected with IUP recordings during labor I is an invasive technique and the catheters are delicate and expensive Biological measuring artefacts such as those caused by a part of the fetus pressing the transducer against the uterine wall cannot always be excluded

The micro-transducer technique seemed to give about the same values for the IUP parameters as previously used methods

The mean value of the resting pressure 13 mm Hg a a mean cervical dilatation of 4 cm was in accordance

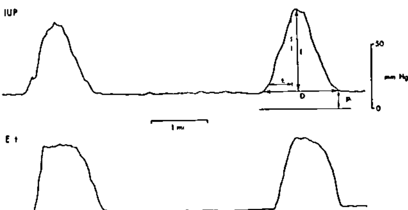


Fig 4 Internal (IUP) and external (Ext) recordings from one of the patients Cervical dilatation 5 cm strong contractions The head of the fetus is just above spina ischiadica

with previous reports (5 9 10 11) The intensity or amplitude 50 mm Hg was somewhat higher than that reported by Kraphol *et al* 1970 (10) and Lindmark *et al* 1975 (11) at the same degree of cervical dilatation The reason for this could be differences in recording techniques It has been observed that with open end catheters the amplitude of the contraction is often reduced (13 14) Extra amniotic accurate IUP determination with these catheters should imply repeated infusions of fluid to create a pool of liquid in which the measuring aperture of the open end catheter is placed (5)

The speed of pressure development during a contraction has been calculated in several ways (5 9 15) Rise time is an accepted term in bio-technical medicine (16) and in our recordings it was easily obtained Our mean value for the pressure rise of the contractions 3 4 mm Hg per second was about the same as that reported by Csapo (5) and by Jenssen (9) Like these authors and Baumgarten 1967 (4) and Lindmark *et al* 1975 (11) we found that with increasing amplitude there was an increase in rise time of the contraction (Table I) The duration of the contraction 76 seconds was somewhat shorter than that

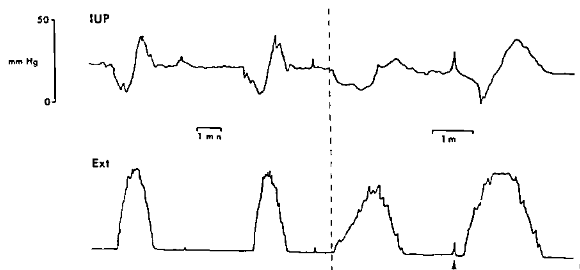


Fig 5 IUP recording in a patient at the initiation of labor Cervical dilatation 3-4 cm membranes intact head presentation The head mobile in the pelvic inlet Upper tracing intrauterine pressure (IUP) recorded approximately 4 cm from the interal os lower tracing external tocography (Ext) When the contraction starts as judged by recording there is a transient decrease in the IUP in lower uterine segment Arrow denotes cough which ser as an in situ test of the equipment

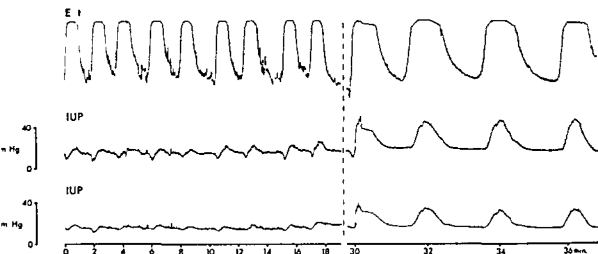


Fig 6 Simultaneous external and IUP recordings from a patient before and after deliberate rupture of the membranes Upper tracing denotes the external tocographic recordings middle tracing IUP about 6 cm from the external orifice bottom tracing IUP just inside the internal orifice The left part of the figure shows the situation at the initiation of labor i e before rupture of the membranes Simultaneous with the start of the contractions there is a small decrease in the IUP in the lower segment (cervical dilatation 3 cm) About 2 hours later (right part of the figure) at a cervical dilatation of 5 cm the membranes are deliberately ruptured The pressure situation is now altered simultaneous with the contraction as recorded by external tocography there is an increase in the IUP at both levels of recording

given in previous reports (10 11) One reason for this could be the way we calculated the duration This way was chosen because we failed to get an acceptable reproducibility with the technique described by Kraphol *et al* 1970 (10)

By the ultrasonic investigation the thickness of the wall and the smallest radius of the uterine could be estimated Since the thickness of the uterine wall showed very small variations we disregarded this factor when calculating the myometrial tension The smallest uterine radius could be determined with high precision by an experienced ultrasonic operator using the compound B scan technique However during labor the multi-element scanner despite its inferior resolution sometimes facilitated determination of the radius

Few attempts to calculate the myometrial tension *in vivo* seem to have been made (1 5 9) Even if the described technique of investigation may be considered somewhat exclusive we think that it could be used in most obstetrical wards where research is carried out In the two subjects in whom induction of labor failed the myometrial tension was lower than in those successfully delivered within eight hours after initiation of labor These findings may imply that a more accurate determination of the myometrial activity during labor is possible with the present technique than with those generally used for IUP recording This can facilitate evaluation of the influences of different drugs used in obstetrics to control uterine activity during labor In addition the present technique might improve the IUP part of intrapartum clinical monitors such as that of the Cardiff infusion system (6 17) This equipment for automatic control of oxytocin induced labor has been suspected to overstimulate the uterus (7 13)

In the 4 patients in whom IUP was recorded in the lower uterine segment (i e 2-4 cm from the internal os) at the very initiation of labor it was observed that simultaneously with the fundal myometrial contraction there was a decrease in the IUP in the lower segment

During labor the shape of the uterus is altered There is a decrease in the diameter of the upper segment and an increase in the diameter of the lower isthmical part (12) According to the law of Laplace an increase in the radius will imply a decrease in the IUP The actual pressure fall was most pronounced at the initation of labor At this time the relatively inelastic intact membranes might not allow accurate transmission of the intra amniotic pressure increase from the upper uterine cavity to the laterally placed micro-transducer in the lower uterine part Therefore because of defective hydrodynamic pressure

transmission and an increase in the isthmic diameter there will be a decrease in the extra amniotic pressure recorded laterally in the lower uterine segment

REFERENCES

1 Anderson A B Turnbull A C & Murray A M The relationship between amniotic fluid pressure and uterine wall tension in preganancy Am J Obstet Gynecol *97* 992 1967

2 Asmussen M Lindström K & Ulmsten U A catheter manometer calibrator A new clinical instrument Biomed Eng *10* 175 1975

3 Asmussen M & Ulmsten U A new technique for measurement of the urethral pressure profile Acta Obstet Gynecol Scand *55* 167 1976

4 Baumgarten K Die Beeinflussung der Uterusmotilität Brüder Hollinek Wien 1967

5 Csapo A The diagnostic significance of the intra uterine pressure Part I and II Obstet Gynecol Surv *25* 403 1970 and *25* 515 1970

6 Francis J G Turnbull A C & Thomas F F Automatic oxytocin infusion equipment for induction of labor J Obstet Gynaecol Br Comm *77* 594 1970

7 Goodlin R C Lowe E W & Douglass R Clinical trial with alarm system labor monitors Obstet Gynecol *44* 281 1974

8 Ingelman Sundberg A & Lindgren L Intra uterine measurement of pressure during labour J Obstet Gynaecol Br Emp *62* 629 1955

9 Jenssen H The shape of the amniotic pressure curve before and after paracervical block during labor Acta Obstet Gynecol Scand Suppl 42 1973

10 Kraphol A J Myers G G & Caldeyro-Barcia R Uterine contractions in spontaneous labor Am J Obstet Gynecol 106 378 1970

11 Lindmark G Induction of labor with prostaglandin $F_2\alpha$ by intravenous infusion Acta Universitatis Uppsaliensis Dissertation No 228 1975

12 Narik G The method of transfer of labour contractions to the contents of the uterus J Obstet Gynaecol Br Emp *66* 58 1959

13 Neves Dos Santos L M Odendaal H J Crawford J W & Henry M J Investigation of some problems associated with the Cardiff infusion pump Br J Obstet Gynaecol *83* 225 1976

14 Odendaal H J Neves Dos Santos L M Henry M J & Crawford J W Experiments in the measurement of intra uterine pressure Br J Obstet Gynaecol *83* 221 1976

15 Tesch P Bolte A Breuker K H & Raabe A Ein neues Verfahren zur quantitativen Analyse der Uterus kontraktionen Perinatale Medizin Bd V p 214 Thieme Stuttgart 1974

16 Truxal J G Automatic feed back control system synthesis Mc Graw Hill Co New York 1955

17 Turnbull A C & Anderson A B Uterine contractility and oxytocin sensitivity during human pregnancy in relation to the onset of labour J Obstet Gynaecol Br Comm *75* 278 1968

18 Ulmsten U Studies on ureteral function in women Thesis University of Lund 1974

19 Ulmsten U Andersson K E & Forman A Relaxing effects of nifedipine on the non pregnant human uterus in vitro and in vivo Obstet Gynecol *52* 436 1978

20 Ulmsten U & Andersson K E Multi-channel intra uterine pressure recording by means of micro-transducers Acta Obstet Gynecol Scand *58* 115 1979

Submitted for publication March 29 1978

Ulf Ulmsten M D
Department of Obstetrics and Gynecology
University Hospital
S-214 01 Malmö
Sweden

Acta Obstet Gynecol Scand 58 555–559 1979

DETERMINATION OF TONICITY IN THE NON PREGNANT HUMAN UTERUS IN VIVO

Ingemar Joelsson and Othon Lalos

From the Department of Obstetrics and Gynecology University of Umeå Umeå Sweden

Abstract The method hysterometry has been designed for the study of the effect upon the uterine muscle of pharmacologically active agents Hysterometry has earlier been used on the pregnant uterus and is now described for the non pregnant situation The capacity of the technique is exemplified with results achieved in a study of the effect of prostaglandin synthetase inhibitors and β receptor stimulating agents during dysmenorrhea

Numerous reports are available regarding the effect upon the human uterus of pharmacologically active agents with stimulating or relaxing properties The direct effect of these agents on the myometrium has mostly been discussed with reference to recordings of intrauterine pressure Various techniques have been employed such as pressure transmitting systems utilizing fluid filled rubber balloons closed or open-end catheters and microtransducer catheters (4 6 7 8 9 16 21) In these studies the changes in intrauterine pressure has been taken to represent the effect of the drug upon the myometrium

The aim of the present investigation has been to apply a technique for the study of the non pregnant human uterus which earlier has been used only on the pregnant uterus (1) This technique utilizes mechanical distension for the induction of muscular response This response which is modified by hormonal environment as well as by pharmacologically active drugs is evaluated If the hormonal condition remains unchanged alterations in muscular response can be used for the quantitative measurement of the drug effect upon the myometrium

TECHNIQUE

The mechanical stimulation of the myometrium is achieved by oscillation of a small quantity of fluid into and out of a thin walled rubber balloon with a basic content of 1 5 – 2 5 ml fluid placed in the uterine cavity Cervical dilatation up to 6 mm diameter was required for the insertion of the balloon

A bellows pump is connected to a transmission tube which ends in a stem with several perforations Fig 1 The balloon is attached around the stem which also contains a cannula tube used for pressure transmission from the inside of the balloon This cannula tube ends in one of the perforations while all the other openings serve as connections between the interior of the stem and the interior of the balloon

The bottom of the bellows is connected to a piston governed by an eccentric This eccentric is mounted on the axis of a shunt wired electrical motor of DC type with constant voltage over the field but not over the armature Variable speed transmissions within the range 0 025 – 6 0 rotations per second is achieved with a thyristorized current control and a two-step mechanical gear The feed back of a tachometer generator ensures constant speed at each setting By means of a mechanical coupling between the bottom of the bellows and a linear precision potentiometer the volume in the balloon as a function of time is monitored on one channel of a dual beam storage oscilloscope The instantaneous pressure in the balloon which does not take any tension is recorded on the other channel of the same oscilloscope by means of a pressure transducer with a membrane of a high degree of stiffness The recorded pressure is considered to be equivalent to the overall pressure inside the cavity of the organ

Hydrodynamic considerations for the dimensioning of the instrument for hysterometry were the following

1 The system shall be totally inelastic and must not contain air or vapor at any time
2 The intracavitary pressure shall be determined correctly

This means that the change of volume within the balloon must be synchronous with the change of volume in the bellows pump In addition pressure losses due

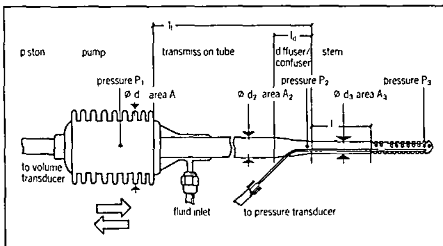


Fig 1 Mechanical device for sinusoidal distension of the uterine wall The thin walled rubber balloon is mounted without leakage around the perforated part of the stem

to friction and/or inertia during movement of the fluid in the system must be reduced to a minimum

Equation systems representing the hydrodynamic prerequisits have been presented in detail elsewhere (12) Briefly the ground volume (V_g) used for the filling of the rubber balloon after its introduction into the uterine cavity was between 1 5 and 2 5 ml In a pilot study significant differences in results were shown to occur first when the ground volume was below 1 0 ml The oscillation volume (V) used for filling and emptying the balloon was 0 4 to 0 8 ml

0 5 ml

experimental set up used for testing the per ce characteristics of the hysterometry equip it was observed that the increase in static pres as a result of the transport of fluid between the bellows pump and a large diameter water filled plastic basin was insignificant Also the resulting change in dynamic pressure was less than 5 mm Hg It made no difference to these results whether the rubber balloon enclosed the stem or not This indicates that the properties of the wall of balloon do not influence the recording of muscular response to distension

Evaluation of the recordings were made on the basis of the following data

1 volume of the fluid used as basic content of the rubber balloon (V_g)

2 the volume of fluid used for the distension of the uterine muscle (V_{osc})

3 the changes in intrauterine pressure (ΔP)

4 *the frequency of distension (f)*

5 the uterine dimensions divided into

a *size of the corpus cavity* (V_i) and

b thickness of the uterine wall (h)

The thickness of the uterine wall has been taken as 1 25 cm this measure was arrived at empirically by measurements of the uterine wall in specimens after hysterectomy When the uterine stem of the hysterometry instrument surrounded by the fluid filled balloon is in place the uterine cavity is — for sake of simplicity — considered to represent a hollow ellipsoid The volume (V_i) of this ellipsoid is

$$V = V_s + V_g$$

where V_s is the volume of the hysterometry instrument

V_i however can also be defined according to the following

$$V = 4/3\ \pi\ r^2\ b$$

In this equation $2b$ is the sound measurement of the corpus compartment and r is the symmetrical rotation radius in an imagined section through the ellipsoid

With the view to obtain a quantity which will serve to characterize the functional state of the myometrium as well as the effect upon it of hormonal and pharmacologically active agents a *tonometric index* of the myometrium is defined In order to arrive at this tonometric index one has to accept several approximations Mechanical distension of the uterine muscle is accordingly considered to be so slight that the intra abdominal extrauterine pressure is not changed during the measurement procedure The uterine wall is furthermore considered to be incompressible *i e* the volume of the uterine wall is the same before and at maximum distension

In the mathematical model used to characterize the *tonometric index only the conditions in an imagined*

section through the rotation ellipsoid at the *symmetrical rotation radius* (r) are studied

$$r = \left(\frac{3\ (V_t + V_{osc})}{4\pi\ b}\right)^{1/2}$$

The *contractile modulus* (m) i e the ratio between the relative strain and the relative contraction of diameter is defined The equation can have the following approximate expression provided the magnitude of the distension is small

$$m \sim \frac{1 - \frac{r}{R}}{\frac{r}{R}\left(1 - \frac{b}{B}\ \frac{r}{R}\right)}$$

R being $(r+h)$ and B being $(b+h)$

As the second step the *tangential stress* (σ_t) in the innermost layer of the uterine wall is estimated In order to obtain equivalent *expressions for pregnant* and non pregnant uteri the imagined section of the rotation ellipsoid is treated as part of a cylinder

$$\sigma_t \approx [P(R^2 + r^2) + P\ 2R^2]\frac{1}{R^2 - r^2}$$

The subscripts in the equation denote t tangential i inner and o outer

In order to eliminate the outer pressure *the stress differences in tangential* ($\Delta\sigma$) *axial* ($\Delta\sigma_x$) and *radial* ($\Delta\sigma$) directions between non distended (σ_{t_0}) and distended conditions (σ_{t_1}) are calculated as the next steps *by the following* equations

$$\Delta\sigma_t = \sigma_{t_1} - \sigma_{t_0}$$

$$\Delta\sigma_t \sim \Delta P\ \frac{1 + (r/R)}{1 - (r/R)^2}$$

and

$$\Delta\sigma \sim \Delta P\ \frac{(r/R)^2}{1 - (r/R)^2}$$

As the distension is small the differences between R_1 and R_0 r_1 and r_0 B_1 and B_0 and b_1 and b_0 are minute

$$\frac{r_1 + r_0}{R_1 + R_0}\ \frac{b}{B} \sim \frac{rb}{RB}$$

Obviously *the stress difference in the radial direction* ($\Delta\sigma$) equals $-\ \Delta P$

The next step is to form an expression for the *tangential strain* (ϵ) Differentiating the equation for the uterine volume

$$V \approx 4/3\,\pi r^2 b$$

gives the relation

$$dV/V = 2dr/r + db/b$$

Two cases can be viewed namely

$db/b = 0$ and the *difference in tangential strain*

$$\Delta\epsilon_t = 0.5(dV/V) = 0.5(V_x/V)$$

when there is an extreme eccentricity of the rotation ellipsoid i e it approximates an cylinder and

$$db/b = dr/r \text{ and } \Delta\epsilon_t = 1/3\,(V_{osc}/V)$$

when the eccentricity equals 1 i e the structure is like a sphere The first relation is used for the non pregnant and the second for the pregnant condition

Finally Hooks law ($\sigma = E\,\epsilon$) is applied which expresses the relation between stress and strain in an elastic material E is the modulus of elasticity and is proposed as the *tonometric index of the myometrium* The equation $E = \sigma/\epsilon$ is valid for an one dimensional structure For a three dimensional structure e g the uterus some corrections have to be made and Hook s law then provides the expression

$$\epsilon_t = \frac{1}{E}\left(\sigma_t - \frac{\sigma + \sigma_x}{m}\right)$$

and

$$E = \frac{\Delta\sigma_t - (1/m)\Delta\sigma_x - (1/m)\Delta\sigma_r}{\Delta\epsilon_t}$$

It must be emphasized that the tonometric index (E)

1 Only mirrors differences between conditions before and at maximal distension
2 Is calculated from the appraisal of a section through the rotation ellipsoid assuming this to be part of a cylinder
3 Pays regard only to the stress in the innermost layer of the myometrium where stresses are maximal

In the present calculation the stress difference in tangential direction has been modified by the influence of stresses in axial and radial directions These influences are however of minor importance

EXAMPLES

Hysterometry has now been used as a tool for the determination of *pharmacological* effect upon the *myometrium* It can be shown that prostaglandin $F_{2\alpha}$ for example increases the myometrial response to mechanical distension considerably and that on the other hand β-receptor stimulating agents decrease the *myometrial response* The latter situation is shown for dysmenorrheic menstruation in Fig 2

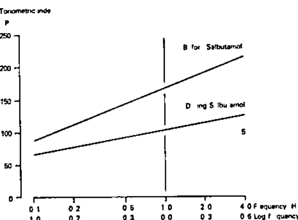


Fig 2 Group (n = 5) regression lines of tonometric indices on logarithm of frequency before (y = 167 + 80x) and during (y = 102 + 37x) Salbutamol infusion in a dose of 10 µg/min

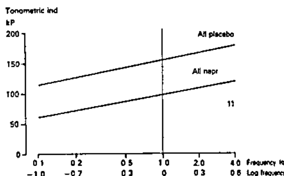


Fig 3 Group (n = 11) regression lines of tonometric indices on logarithm of frequency of stimulation in dysmenorrheic women treated with placebo (y = 154 + 41x) and naproxen (y = 99 + 40x)

The effect of naproxen on the uterine tonicity in eleven dysmenorrheic women has been tested with the same hysterometric technique (13) Hysterometry was performed on the first day of each of two consecutive menstrual periods and uterine tonicity was evaluated Uterine tonicity on the first menstrual day was found to be high in all women during the placebo treated menstruation Naproxen sodium and naproxen acid significantly decreased the uterine tonicity and re ed pain in ten of the eleven women who received 11th woman showed no decrease of uterine neither did she report any relief of pain The difference between intercepts of regression quations representing the placebo and the naproxen treatment situations respectively were statistically significant 0 001 < p < 0 01

DISCUSSION

The mechanical behaviour of the uterine wall in vivo has been hampered by the difficulty in using monitoring techniques that allow exact determination of the volume pressure relationship (2 7 8 9 11) Development in the field of uterine dynamics might be promoted by the application of methods for the study of action and membrane potentials preferably simultaneously with hysterometry and with recording of spontaneous activity (20)

Hysterometry is a technique for the study of hormonal and pharmacological influences upon the myometrium The primary data registered are changes in pressure differences between non distended and distended conditions in relation to the contraction of the myometrium excited by distension These data are transformed into tonometric indices of the myometrium As tonometric indices are bound to the frequency of stimulation the experimental results are evaluated in terms of coefficients of regression equations of indices upon the logarithm of frequency of stimulation The intercept of such equation has been considered to express the degree of uterine tonicity If the numerical value of an intercept alter as a function of changes in the hormonal environment or the availability of pharmacological active agents such alternation might be used for the quantification of the effect Group lines might be formed and confidence limits calculated In the mathematical formulas provision is made for individualisation with respect to size of the uterus and the thickness of the muscular wall Although the technique of hysterometry does enable one to compare pharmacological effect amongst individuals an effort has been made always to quantify effect from intra rather than inter individual comparisons

REFERENCES

1 Anzen B Hysterometry — a method for *in vivo* determination of pharmacologic effect on the myometrium Thesis Stockholm 1977

2 Apter J T & Graessley W W A physical model for muscular behavior Biophys J *10* 539 1970

3 Bengtsson L Ph Hormonal effects on human myometrial activity *In* Vitamins and hormones Vol 31 p 257 1973 Academic press New York

4 Bengtsson L Ph The sponge tipped catheter a modification of the open end catheter for recording myometrial activity in vivo J Reprod Fertil *16* 115 1968

5 Bozler E An analysis of properties of smooth muscle Cold Spring Harbor Symp Quant Biol *9* 260 1936

6 Cibils L A Contractility of the non pregnant human uterus Obstet Gynecol *30* 441 1967

7 Coutinho E M Uterine activity in non pregnant women *In* Proceedings of VIII Conference of International Planned Parenthood Federation (ed R K B Hankinson R L Kleinman and P Eckstein) p 432 London 1967

8 Csapo A I The diagnostic significance of the intrauterine pressure Part I and II Obstet Gynecol Surv *25* 403 1970 and *25* 515 1970

9 Hendricks C H A new technique for the study of motility in the non pregnant human uterus J Obstet Gynecol Br Comm *71* 712 1964

10 Joelsson I In vivo determination and cyclic variability of uterine volum Acta Obstet Gynecol Scand *51* 197 1972

11 Joelsson I Mechanics of human myometrium studied with dynamic tests in vivo Acta Obstet Gynecol Scand *51* 127 1972

12 Joelsson I Gidlund L Anzen B & Ingelman Sundberg A In vivo determination of stress strain relation of the human myometrium Acta Obstet Gynecol Scand *55* 325 1976

13 Joelsson I & Lalos O The effect of inhibitors of prostaglandin synthesis in primary dysmenorrhes studied with hysterometry Acta Obstet Gynecol Scand Suppl *87* 45 1979

14 Krall J F & Korenman S G Mechanisms in the control of uterine contractility Adv Sex Horm Res *3* 75 1977

15 Little R C Dynamics of stress relaxation in skeletal muscle Am J Physiol *217* 1665 1969

16 Moawd A H & Bengtsson L Ph In vivo studies of motility patterns of the non pregnant human uterus Am J Obstet Gynecol *98* 1057 1967

17 Pauerstein C J & Zauder H L Autonomic innervation sex steroids and uterine contractility Obstet Gynecol Survey *25* 617 1970

18 Roth Brandel U Bygdeman M & Wiqvist N Effects of intravenous administration of prostaglandin E and $F_{2\alpha}$ on the contractility of non pregnant human uterus in vivo Acta Obstet Gynecol Scand 49 Suppl *5* 19 1970

19 Rüegg J C Smooth muscle tone Physiol Rev *51* 201 1971

20 Wolfs G M J A & van Leeuven M Electromyographic observations on the human uterus during labour Acta Obstet Gynecol Scand Suppl 90 1979

21 Åkerlund M Bengtsson L Ph & Ulmsten U Recording of myometrial activity in the non pregnant human uterus by a microtransducer catheter Acta Obstet Gynecol Scand *57* 429 1978

Submitted for publication February 2 1978

Othon Lalos M D
Department of Obstetrics and Gynecology
The University Hospital
S-901 85 Umeå Sweden

ANNOUNCEMENT

INTERNATIONAL AND NATIONAL CONGRESSES 1980 – 1981

Date	Place	Name	Office
1980			
June July 30–2	L Aquila Italy	International Symposium on Oligozoospermia	G Frajese Clin Med V–Policlinico Umberto I–00100 Roma Italy
June July 30–3	Leuven Belgium	Gynecological microsurgery A practical course	Dr W Boeckx Centre for Microsurgery Academic Hospital St Rafaël 3000 Leuven Belgium
July 3–5	Bordeaux France	International Sympo ium on IUD Technology	Dr Karl-Gösta Nygren University Hospital S–75014 Uppsala Sweden
July 4–6	Toulouse France	6th International Symposium on Sex Education	C I F R E S 17 Rue de Nimes 31400 Toulouse France
July 5–11	Madrid Spain	Xth World Congress on Fertility and Sterility	Congress Secretariat Calle San Bernardo 5 Madrid Spain
July 8–11	Edinburgh England	22nd British Congress of Obstetrics and Gynaecology	Royal College of Obstetricians & Gynaecologists 27 Sussex Place Regent s Park London NW1 4RG England
September 2–5	Barcelona Spain	7th European Congress of Perinatal Medicine	Congress secretariat Apt de Correos no 29015 Barcelona Spain
September 2–6	Berlin Germany	6th International Congress of Psychosomatic Obstetrics and Gynecology	Ass Prof Dr M Stauber Frauenklinik Charlottenburg der FUB Pulsstr 4 D 1000 Berlin 19 W Germany
September –7	Kiwah Island Charleston SC	International Symposium on Carcinoma of the Cervix Biology Etiology & Diagnosis	E S E Hafez M D OB/GYN Wayne State University Medical Res Bldg 550 E Canfield Detroit MI 48 01 USA
ber –16	Bologna Italy	First International Symposium on Recent Advances in Prenatal Diagnosis	A C Assistanza Congressi Via P Palagi 21–40138 Bologna Italy
September 24–27	Kiel West Germany	Embryo Transfer and Instrumental Insemination	Professor Kurt Semm Abteilun Frauenhei lkunde Hegewischstrasse 4 D 2300 Kiel 1 W Germany
September 29–30	Freiburg Germany	International Congress on Endocrinology of Human Infertility	C Ferrari M D P O Box 995 Milan Italy
November 18–23	New Orleans Louisiana USA	Clinical Symposium on Gynecologic Endoscopy	American Association of Gynecologic Laparoscopists 11239 South Lakewood Boulevard Downey California 90?41
December 1–12	Melbourne Australia	Seventh UICC Training Course in Cancer Research	Dr A W Burgess UICC Course The Walter and Eliza Hall Institute Royal Melbourne Ho p P O 3050 Victoria Australia
1981			
January 26–31	Mexico City Mexico	Pan American Congress of Andrology	Gerald Bagazinski Congr Admin 31600 West Chicago Livonia MI 48150 USA
March 22–26	West Berlin West Germany	IIIrd World Congress of Human Reproduction	Dozent L Mettler Frauenklin der Univ Hegewischstr 4 D 2300 Kiel 1
June 9–12	Ostend Belgium	Third International Congress on the Menopause	The International Menopause Society 8 av Don Bosco 1150 Brussels Belgium

Acta Obstet Gynecol Scand 58 561–564 1979

QUINACRINE HYDROCHLORIDE

Review and mode of action of an antimalarial used as an occlusive agent for transvaginal human sterilization

Eva Patek

From the Department of Obstetrics and Gynecology Karolinska Institutet Huddinge University Hospital Huddinge Sweden

Abstract Quinacrine hydrochloride mainly used as an anti malarial has been used as a nontoxic chemosterilant in a transvaginal procedure in the human female Clinical ex periments indicate that Quinacrine acts as a powerful obstructive agent exclusively on the epithelium of the intra mural portion of the tube without alterating the histology of the endometrium

The precise mechanism of Quinacrine s obstructive action on the mucosa of the uterotubal junction is unknown

Its possible mode of action is binding to epithelial DNA thus forming a clot of granulomatous tissue as Quinacrine is known to form adhesions when used in the control of neo-plastic effusions

Zinc is known to inhibit Quinacrine DNA binding The human endometrium rich in Zinc is unaffected by Quina crine whereas the tubal cornua with little Zinc promote the obstruction by Quinacrine DNA bondage

The procedure is effective in 90 per cent of the cases with two instillations of Quinacrine Further studies are essential to find agents that would potentiate the action of Quinacrine on the human Fallopian tube epithelium

In the search for a transvaginal technique of steriliza tion of women where a nontoxic watersoluble sub stance could be applied directly into the uterine cavi ty Jaime Zipper in Santiago di Chile has made exten sive studies on the effect of various cytotoxic agents (42) He wanted a compound which would have a rather specific and selective effect upon the epithel ium of the intramural portion of the Fallopian tubes and which would be relatively innocuous if it came in contact with the peritoneum by escape from the tubes and to this effect he used a saturated solution of Quinacrine hydrochloride prepared in sterile distilled water Originally a 4 ml suspension contain ing 1 g of the drug was instilled through a biopsy can nula introduced to the top of the endometrial cavity (45) Later trials with more saturated solutions of Quinacrine were undertaken and and he also studied the effects of chelating agents and other compounds which would enhance the occlusive action of Quina crine (40 44) The procedure proved effective in 65 per cent of cases but had to be repeated once in 35 per cent in order to obstruct the tubes A cumulative obstructive effect took place and in 90 per cent of the cases no patency of the tubes existed after repeat in sufflation and hysterosalpingography

Spontaneous reversibility occured infrequently and only during the first year of treatment Experi ments in rats however (43) have shown that the hy perplastic reaction in the intramural portion of the tubes can be reversed by the administration of either an estrogen or a progesterone Zipper suggests that it may be possible to reverse the reaction in the human as well as in the rat by the systemic administration of either estrogens or progesterons or perhaps by a combination of both If tubal patency can be restored clinically then this procedure which was originally developed as a technique for nonsurgical female sterilization could become a reversible method of contraception easily performed by paramedical per sonnel with minimum danger to the patient

MATERIAL AND METHODS

Pharmacology Quinacrine hydrochloride (Quinacrine Atebrin/e/ Mepacrin/e/) is a bright yellow odourless crystalline powder with a bitter taste Mol wt = 508 9 The compound is a derivate of acridine and has been used in the treatment of malaria since 1930 It has also been used as a remedy for at least thirty different ailments and its tox icology has been studied most extensively (9 12 26 27 29 33) The LD_{50} of Quinacrine hydrochloride for rats is 900 mg per kilogram at parenteral (stomach tube) administra tion (36) The LD_{50} for the intraperitoneal route for rats has not been estimated but the experiments of Keeler *et al* (21) show that it is approximately 250 mg per kilogram They also described the development of enteromegaly and steatorrhea in the rat following intraperitoneal Quinacrine hydrochloride

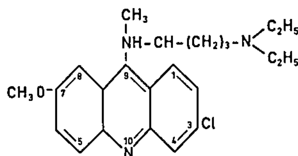


Fig 1 Quinacrine chloride

Morphological changes The Fallopian tubes from 4 of Zipper s patients were removed one year after Quinacrine instillation by salpingoectomy and the tubes were sectioned serially and studied microscopically (45) The histological changes were most marked in the cornual portion of the tubes and diminished rapidly and progressively for a distance of 2 3 mm The remaining portions of the tubes were found to be normal Within the affected area the lumen was obstructed by granulomatous fibrous tissue consisting of lightly stained cells having regular normal nuclei No significant abnormalities were detected in the tubal musculature and Zipper found little effect upon the endometrium So the antifertility effect of Quinacrine hydrochloride is attributable to mechanical obstruction of the cornual portions of the Fallopian tubes (20 34 45)

RESULTS

Effect on carcinomatosis Since the beginning of the s Quinacrine hydrochloride has been used for control of recurrent neoplastic effusions The to this treatment has been favorable (6 7 8 35 38) By local instillation into serous cavities Quinacrine produced an inflammatory reaction resulting in adhesions that partially or completely obliterated the serous cavities Quinacrine hydrochloride is cytotoxic to a variety of normal and tumor cells grown in tissue culture but *in vivo* experiments show that the effect is mainly the production of serositis The maintenance dosage varies according to the Council on Drugs (6) from 200 mgs to 1 g daily depending on the location of the effusion (pleura or peritoneum) and the continued tolerance of the patient

Biochemical effect Whitehouse and Boström (39) have found that Quinacrine hydrochloride significantly uncouples oxidative phosphorylation and Hemker and Hülsmann (14) have confirmed Hellerman s view (13) that Atebrin (Quinacrine) exhibits the relatively unspecific activity of a nonspecific enzyme inhibitor acting by binding generally with proteins

Specific effect on DNA It is well known that Quinacrine hydrochloride forms a molecular complex with DNA (22) The acridine ring of the molecule is intercalated between the base pairs of double helical DNA (23 25) and the aliphatic diamine side chain apparently bridges complementary DNA strands across the minor groove by ionic attraction to phosphate groups (1)

Consequences of the reaction of Quinacrine hydrochloride with DNA are *i)* inhibition of the enzymatic hydrolysis of DNA (22) and *ii)* inhibition of the DNA dependent DNA and RNA polymerase reactions (1)

Biophysical studies on the nature of the Quinacrine DNA complex (22 25) in addition to reports on inhibitions of DNA dependent enzymatic reactions by the drug (1 22) are consistent with the view that the mechanism of biological action of the drug is the specific reaction of Quinacrine hydrochloride with native double stranded DNA This is also confirmed by the experiments of Ciak & Hahn in Washington (5) on the effects of Quinacrine on whole bacterial cells of E coli They found that the resulting mode of action is an impairment of DNA replication and at a cytocidal concentration of RNA transcription

Irvin & Irvin (16 17 18 19) have found evidence for a reversible interaction of Quinacrine with nucleotides using spectrophotometric studies They have also postulated that the side chain of Quinacrine hydrochloride is not an absolute requisite for the interaction of the compound with nucleoproteins

Investigations have been made by Mortland *et al* (28) on the absorption spectra of various basic dyes including the aminoacridines with nucleic acids They found a formation of a dye acid complex joined by more than simple electrostatic attractions The complex binding is stronger for those acridines which have been shown to have an affinity for cell nuclei *in vivo* The dye is more tightly bound to DNA than to RNA

The affinity of Quinacrine for DNA has been used by Caspersson and collaborators (3 4) to identify chromosomes They found that Quinacrine mustard effects selective discrete fluorescent labelling of both plant and mammalian chromosomes Chemically reactive loci may be differentiated along the linear axis of chromosomes by the use of ultramicrofluorometric techniques in combination with ultramicrospectrophotometric determination of the pattern of DNA distribution Thus the Quinacrine-DNA complex can be used for the labelling and identification of

individual chromosomes

Efforts have been made to assay Quinacrine in biological material (2 37) mainly by spectrophotofluorometric methods However no accurate method exists to measure the content of DNA Quinacrine in individual cell nuclei (30 31) Thus the Quinacrine DNA complex is still incompletely understood

DISCUSSION

The effect of trace elements on the Quinacrine DNA complex Trace elements are known to act as co-factors and cation antagonists in different enzyme systems (46) Studies by Hagenfeldt *et al* (10 11) indicate that the human endometrium is rich in Zinc The Zinc content of the endometrium also shows a cyclic behaviour This is in contrast to the endosalpingeal levels of Zinc which Patek & Hagenfeldt (32) found to be considerably lower and totally lacking cyclic changes

The binding of Quinacrine to DNA in the intramural epithelium of the tube is dependent on the relatively rich content of Zinc in the endometrium and its more sparse content in the tubal mucosa The relatively low concentrations of Zinc in the endosalpinx compared with that of the endometrium might be due to different levels of Zinc metalloenzymes e g carbonic anhydrase and alkaline phosphatase Further studies on these enzyme levels are necessary to find agents that could potentiate the occlusive action of Quinacrine hydrochloride on the intramural portion of the human Fallopian tube

REFERENCES

1 O Brien R I Olenick J G & Hahn F E Reactions of Quinine Chloroquine and Quinacrine with DNA and their effects on the DNA and RNA polymerase reactions Proc Nat Acad Sci US *55* 1511 1966

2 Brodie B B Udenfriend S Dill W & Downing G The estimation of basic organic compounds in biological material J Biol Chem *168* 311 1947

3 Caspersson T Farber S Foley G E Kudynowsky J Modest E J Simonsson E Wagh U & Zech L Chemical differentiation along metaphase chromosomes Exptl Cell Res *49* 219 1968

4 Caspersson T Zech L Modest E J Foley G E Wagh W & Simonsson E DNA binding fluorochromes for the study of the organization of the metaphase nucleus Exptl Cell Res *58* 141 1969

5 Ciak J & Hahn F E Quinacrine (Atebrin) Mode of action Science *156* 655 1967

6 Council on Drugs An agent for the palliative treatment of neoplastic effusions Quinacrine (Atabrine) Hydrochloride JAMA *195* 1130 1966

7 Dollinger M R Krakoff I H & Karnofsky D A Quinacrine in the treatment of neoplastic effusions Am Intern Med *66* 249 1967

8 Gellhorn A Zaidenweber J Ultman J & Hirschberg E The use of Atabrine (Quinacrine) in the control of recurrent neoplastic effusions Dis Chest *39* 165 1961

9 Goodman L S & Gilman A *The Pharmacological Basis of Therapeutics* 2nd edition Quinacrine pp 1167 1173 The Macmillan Co New York 1956

10 Hagenfeldt K Plantin L-O & Diczfalusy E Trace elements in the human endometrium 1 Zinc copper manganese sodium and potassium concentrations at various phases of the normal menstrual cycle Acta Endocr *65* 541 1970

11 Hagenfeldt K Plantin L-O & Diczfalusy E Op cit 2 Zinc copper and manganese levels in the endometrium cervical mucus and plasma Acta Endocr 72 115 1973

12 Hecht G Pharmakologisches über Atebrin Arch Exp Path *170* 328 1933

13 Hellerman L Lindsay A & Bovarnick M P Flavoenzyme catalysis Inhibition of d aminoacid oxidase by competition with flavin adnine-dinucleotide of Atabrine (Quinacrine) Quinine and certain other compounds J Biol Chem *163* 553 1946

14 Hemker H C & Hülsmann W C Inhibition of enzymes by Atebrin Biochim Biophys Acta *44* 175 1960

15 Hickman J A & Jones M C Treatment of neoplastic pleural effusions with local instillations of Quinacrine (Mepacrine) Hydrochloride Thorax *25* 2 6 1970

16 Irvin J L & Irvin E M The interaction of antimalarials with nucleic acids I Acridine Science *110* 426 1949

17 Irvin J L & Irvin E M Apparent ionization exponents of homologs of Quinacrine Electrostatic effects J Am Chem Soc *72* 2743 1950

18 Irvin J L & Irvin E M The interaction of a 9 aminoacridine derivative with nucleic acids and nucleoproteins J Biol Chem *206* 39 1954

19 Irvin J L & Irvin E M The interaction of Quinacrine with adenine nucleotides J Biol Chem *210* 45 1954

20 Israel R Current concepts in female sterilization Clin Obstet Gynecol *17* 139 1974

21 Keeler R Richardson H & Watson A J Enteromegaly and steatorrhea in the rat following intraperitoneal Quinacrine (Atabrine) Lab Invest *15* 1253 1966

22 Kurnick N B & Radcliffe I E Reaction between DNA and Quinacrine J Lab Clin Med *60* 669 1962

23 Lerman L S Structural considerations in the interaction of DNA and acridines J Molec Biol *3* 18 1961

24 Lerman L S The structure of the DNA acridine complex Proc Nat Acad Sci US *49* 94 1963

25 Lerman L S Acridine mutagens and DNA structure J Cell Comp Physiol *64* 1 1964

26 Martindale s Extra Pharmacopoeia 25th Ed Mepacrine Hydrochloride (ed Norman W Blackow) pp 326-328 London 1972

27 Merck Index 8th Ed Quinacrine Hydrochloride p

MSD 1968

28 Morthland F W De Bruyn P P H & Smith N H *Spectrophotometric studies on the interaction of nucleic* acids with aminoacridines and other basic dyes Exptl Cell Res 7 201 1954

29 Møller K O Mepakrin *In* Farmakologi 5 Udgave p 114 Nyt Nordisk Forlag Arnold Busck København 1958

30 Patek E Some cytochemical properties of isolated human endosalpingeal cells Acta Cytol *18* 414 1974

31 Patek E The epithelium of the human Fallopian tube A surface ultrastructural and cytochemical study Acta Obstet Gynecol Scand Suppl 31 1974

32 Patek E & Hagenfeldt K Trace elements in the human Fallopian tube epithelium Copper Zinc Manganese and Postassium in the menstrual cycle Int J Fertil *19* 85 1974

33 Paramacopoea Nordica Editio Svecica Vol II Mepacrini chloridum pp 362 365 Apotekarsocitetens förlag Stockholm 1964

34 Porter C W Jr & Hulka J F Female sterilization in current clinical practise Fam Plann Perspect *6* 30 1974

35 Rochlin D B Smart C R Wagner D E & Silva A R M The control of recurrent malignant effusions using Quinacrine hydrochloride Surg Gynecol Obstet 991 994 May 1964

36 Siegel H & Mushett W Structural changes following administration of Quinacrine hydrochloride Arch Path *38* 63 1944

37 Udenfriend S Duggan D E Vasta B M & Brodie B B A spectrophotofluorometric study of organic compounds of pharmacological interest J Pharmacol Exptl Therap *120* 26 *1957*

38 Ultman J E Gellhorn A Osnos M & Hirschberg E The effect of Quinacrine on neoplastic effusions and of their enzymes Cancer (Philad) *16* 283 1963

tehouse M W & Boström H Biochemical pro- *of anti inflammatory drugs VI The effects of* ...hloroquine (Resochin) Mepacrine (Quinacrine) and some of their potential metabolites on cartilage metabolism and oxidative phosphorylation Biochem Pharmacol *14* 1173 1965

40 Zipper J A & Insunza S Pharmacological agents that potentiate or inhibit the occlusive action of Quinacrine *in the rabbit tube and rat uterus In Female Sterilization* (eds G W Duncan R D Falb and J J Speidel) pp 131 137 Academic Press New York & London 1972

41 Zipper J A Medel M Pastene L Rivera M & Tatum H J *Human fertility control* by use of *trace elements* *In* Control of human fertility Proc 15th Nobel Symposium (eds E Diczfalusy and U Borell) Almqvist & Wiksell Uppsala 1971

42 Zipper J A Medel M Pastene L & Rivera M Intrauterine instillation of chemical cytotoxic agents for tubal sterilization and treatment of functional metrorrhagias Int J Fertil *14* 280 1969

43 Zipper J A Prager R & Medel M Biological changes induced by unilateral intrauterine instillation of Quinacrine in the rat and their reversal by either estradiol or progesterone Fertil Steril *24* 48 1973

44 Zipper J A Stachetti E & Medel M Esterilizacion Feminina Presentado en Bogota 24 5 4 6 1971 Personal communication

45 Zipper J A Stachetti E & Medel M Human fertility control by transvaginal application of Quinacrine on the Fallopian tube Fertil Steril *21* 581 1970

46 Zipper J A Medel M Pastene L & Rivera M Human fertility control through the use of endouterine metal antagonisms of trace elements (EMATE) *In* Control of Human Fertility (eds E Diczfalusy and *U* Borell) pp 199 218 Almqvist & Wiksell Stockholm 1970

Submitted for publication March 9 1978

Eva Patek M D
Department of Obstetrics and Gynecology
Huddinge Hospital
S 141 86 Huddinge
Sweden

Acta Obstet Gynecol Scand 58 565–567 1979

CASE REPORT

VULVAL EOSINOPHILIC GRANULOMA

M Miodovnik R Adatto A Adoni Z Palti and L Dollberg

From the Department of Obstetrics and Gynecology Hadassah University Hospital Mount Scopus
and the Department of Pathology Shaare Zedek Hospital
Jerusalem Israel

Abstract A case of *Eosinophilic Granuloma* of the vulva associated with *Diabetes Insipidus* is presented

There is neither specific nor adequate treatment for the vulval lesions Treatment with local steroids should first be tried If this does not help Roentgen ray irradiation should be given Simple vulvectomy is a last resort with poor results

Eosinophilic Granuloma of the vulva is a rare disease and belongs to the group of *Histiocytosis* X Recently the term *Multifocal Eosinophilic Granuloma* has been suggested (1 2) Skeletal *Eosinophilic Granuloma* has been extensively reported (3) but vulval lesions are most uncommon The relatively high incidence of *Diabetes Insipidus* in association with vulval *Eosinophilic Granuloma* has been recorded which further indicates the relationship of *Eosinophilic Granuloma* of the vulva with other members of the *Histiocytosis* X group

Here we present another case of *Eosinophilic Granuloma* of the vulva in which *Diabetes Insipidus* preceded the vulval lesions by some 20 years

CASE REPORT

The patient was a 51 years old married Jewish woman para IV born in Iran and living in Israel for 11 years She had had a hysterectomy 13 years ago because of post partum hemorrhage She was referred to the out patient clinic because of itching and swelling of the vulva for the past few years Examination revealed ulcerated nodules measuring 0 5 – 1 5 cm situated near the clitoris and on the labia majora and minora (Fig 1) She was treated with local and systemic antiobiotics and steroid creams for three months without benefit then a biopsy specimen from one of these lesions was taken after a year of treatment without improvement she was admitted to the department of gynecology On examination on the vulva there were ulcerated nodules The hard palate showed small granulomatous erosions to each side of the midline In the ^{99}mTc-ethane 1 hydroxy 1 diphosphonate bone scan there was an area of increased uptake in the base of the skull Roentgen rays did not show pathology in this area The mandibules showed granulomas around the teeth on both rami but no destruction of bone During the hospitalization it was noticed that daily amounts of urine were 4-5 liters The patients on questioning reported that she suffered from polyuria and thirst for the last twenty years but she had never complained of this to the physician before A diagnosis of *Diabetes Insipidus* was made and confirmed by Pitressin and water deprivation tests

A second vulval biopsy and a biopsy from the hard palate were performed The patient refused treatment by Roentgen ray irradiation and because itching was intolerable a simple vulvectomy was performed The postoperative course was uneventful Three months later there was a recurrence of the skin lesions in the perianal region She refused further hospitalization and treatment

The histological findings were similar in all the specimens Macroscopically the specimen showed many ulcerations alternating with elevated areas resulting in geographic configuration There was a narrow margin of normal tissue

Histologically there were large areas with proliferating histiocytes a variable number of eosinophils and small



Fig 1 Distorted and eczematous labia majora and adjacent tissue The surface shows white papulation and small area of erosion

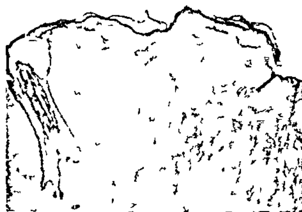


Fig 2 Vulva proliferating histiocytes both deep and superficial ulceration and secondary inflammation
HE×36 (10×3 6)



Fig 4 Vulva granuloma like nodule with diffuse proliferation of histiocytes in dermis and chronic inflammation Invasion of epidermis by histiocytes
HE×144 (40×3 6)

abscess formation The histiocytes showed pale irregularly shaped nuclei and substantial slightly vacuolar or granular eosinophilic cytoplasm often with poorly defined borders (Fig 2 3) There was an occasional mitotic figure A few giant cells were also seen The histiocytes were found both deep in the subcutaneous tissues and more superficially closely apposed to the epidermis Ulceration would appear to have been formed in two ways due to histiocyte infiltration and pressure necrosis of the epidermis or due to invasion of the epidermis by individual cells as well as in nestlike groups The histiocytes occupied large areas in the dermis in the form of sheets as well as in small granuloma like nodules (Fig 4) There was also dense infiltration of asm cells lymphocytes and follicles No foreign s ova or parasites were found The previous biopsy as perianal tissue taken at the time of the vulvectomy a similar picture

sinophilic Granuloma of the vulva was diagnosed The ingival biopsy revealed the same typical features (Fig 5)

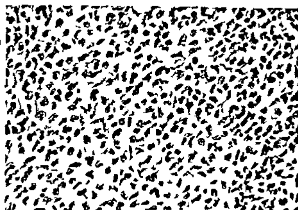


Fig 3 Vulva proliferating histiocytes
HE×360 (100×3 6)

DISCUSSION

Literature on *Eosinophilic Granuloma* involving the vulva is sparse The first case report was published in 1939 by Lane and Smith (4) Since then twelve more case reports have been published (5) Of the seventeen patients twelve also suffered from *Diabetes Insipidus* and thirteen also had lesions in other parts of the body Apart from skin and mucosal lesions in various locations the additional lesions were mostly skeletal (4-9) or sometimes in the lungs (5 10) Curtis and Cawley (11) presented a case of *Eosinophilic Granuloma* of the vulva in a sixteen month girl and McKay (9) presented a case of *Eosinophilic Granuloma* and *Diabetes Insipidus* in a 57 year old woman The vulval lesions were symmetrical they tended to be exudative in children but in the adult they appeared as local nodules (9)

The relatively high frequency of *Diabetes Insipidus* in association with *Eosinophilic Granuloma* may be due to the presence of histiocytosis X infiltration within the hypophysis

The histological picture of the rare vulval eosinophilic granuloma is characteristic and is similar to the well known picture of *Eosinophilic Granuloma* in bone Additional features are the invasion of the epidermis the formation of subepidermal lacunae and eventual ulceration Secondary chronic inflammatory changes were a prominent feature of this case possibly as part of the process by mainly caused by secondary irritation If the inflammatory reaction does not overwhelm the typical picture the histological diagnosis of *Eosinophilic Granuloma* is

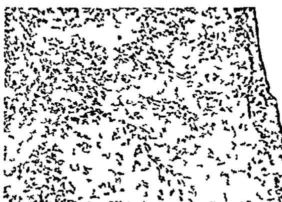


Fig 5 Gingiva sheets of proliferating histiocytes with eosinophils
HE x 360 (100 x 3 6)

not difficult to make The epidermal invasion both by single and by nest like groups of histiocytes should be differentiated from the picture seen in amelanotic malignant melanoma

The etiology of histiocytosis X is unknown and there is neither specific nor adequate treatment for the vulval lesions It is not of bacterial origin but if secondary infections occurs antibiotics may improve the condition Application of steroids locally has been tried with little success *Eosinophilic Granuloma* lesions are sensitive to Roentgen rays and treatment by irradiation should be tried (9) Surgery usually gives good temporary results (9) but our patient hardly benefitted from this procedures itching and lesions soon recurred

In conclusion the diagnosis of vulval *Eosinophilic Granuloma* should be made by biopsy Treatment with local steroids should first be tried and if this *does not help* Roentgen ray irradiation should be given Simple vulvectomy is a last resort with poor results

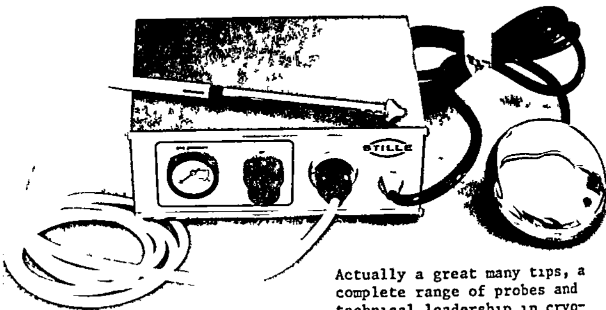
REFERENCES

1 Lieberman P H Jones C R Dargeon H W & Begg C F A reappraisal of eosinophilic granuloma of bone Hand Shüller Christian syndrome and Letterer Siwe syndrome Medicine *48* 375 1969
2 Zinkham W H Multifocal eosinophilic granuloma Am J Med *60(4)* 457 1976
3 Lichtenstein L & Jaffe H L Eosinophilic granuloma of the bone with report of a case Am J Pathol *16* 595 1940
4 Lane C W & Smith M G Cutaneous manifestation of chronic (idiopathic) lipoidosis (Hand Shüller Christian Disease) Arch Derm Syph *39* 617 1939
5 Borglin N E Söderström J & Wehlin L Eosinophilic granuloma (Histiocytosis X) of the vulva Br J Obstet Gynecol Comm *73* 476 1966
6 Woringer F Granulome éosinophilique de la vulve Bull soc franc Derm Syph *66* 375 1959
7 Duperrat B & Rappaport R Granulome eosinophile de la vulve avec longe precession de diabete insipide Bull soc franc Derm Syph *66* 538 1959
8 Woringer F & Peyron M Evolution d un granulome eosinophile de la vulve Bull soc franc Derm Syph *70* 703 1963
9 McKay D G Street R B & Benirschke K Eosinophilic granuloma of the vulva Surg Gynecol Obstet *96* 437 1953
10 Roland A S & Werdinger W F Recurrent spontaneous Pneumothorax New England J Med *270* 73 1964
11 Curtis A C & Cawley E P Eosinophilic granuloma of bone with cutaneous manifestation Arch Derm Syph *55* 810 1947
12 Kierland R B & Epstein J G Eosinophilic granuloma of skin and mucous membrane AMA Arch Derm *75* 45 1957
13 Janovski N S & Douglas C P Disease of the vulva p 105 Harper & Row Publishers Hagerstown Maryland 1972

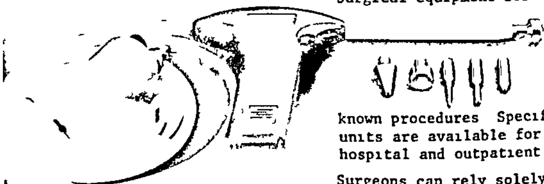
Submitted for publication July 5 1977

M Miodovnik M D
Department of Obstetrics and Gynecology
Shaare Zedek Hospital
Jerusalem
Israel

Spembly has a little tip for all cryosurgeons



Actually a great many tips, a complete range of probes and technical leadership in cryosurgical equipment for all



known procedures Specific units are available for office, hospital and outpatient uses

Surgeons can rely solely on Spembly for four solid reasons

- excellence of equipment performance and design
- world wide experience and distributor network
- comprehensive technical and instructive literature
- and the knowledge that Spembly is continually developing cryosurgical applications and techniques

f you would like more information and literature on the Spembly range
lease contact your local Spembly supplier or write to us in Andover
pembly Limited, Newbury Road, Andover, Hampshire SP10 4DR, England
Telephone (0264)65741 Telex 47403

r to **STILLE**

EDEN AB STILLE-WERNER, Box 43051, S-100 72 Stockholm
INLAND OY STILLE AB, Nervanderinkatu 5 D, SF-00100 Helsinki 10
ORWAY STILLE A S, Postboks 61 Leirdal, Oslo 10
WITZERLAND STILLE AG, Postfach, CH-8038 Zürich

Spembly

FIRST CHOICE IN CRYOSURGERY

Acta Obstet Gynecol Scand 58 569–570 1979

LETTER TO THE EDITOR

BED REST DID NOT PREVENT PREMATURITY IN TWINS BECAUSE THE ETIOLOGY LIES IN THE STRETCH AND POOR PROGESTERONEGENESIS

M O Pulkkinen and M Grönroos

From the Department of Obstetrics and Gynecology Turku University Turku Finland

Sir

The debate concerning the prevention of prematurity in twin pregnancies has become intensified not only here in Scandinavia (1 9) but also in other parts of the world (4 5 6 10) Controversial findings have been reported regarding the efficacy of bed rest during the last trimester of twin pregnancies (1 4 5 6 7 9 10) not to mention the benefit/effort ratio in the economic sense

We therefore made a survey of 235 twin deliveries From 1973 we had a regimen of bed rest for expected twins during the critical weeks 32 36 combined with β mimetic drugs The program was slightly modified in 1978 when patients were allowed home during the week end *In this study bed rest was not found to* have any effect on the weight of the baby in twin pregnancies although retrospective epidemiological studies had to be evaluated critically (Table I)

The average age of the mother parity and the weight of single babies used as controls are given in Table I The selection of patients for bed rest or for non bed rest at week 32 was a question of formal policy (years 1971 – 1972 no bed rest 1973 – 1977 bed rest 1978 bed rest but home week-ends) but some irregularities owing to patients predilections or supposed uterine contractions could not be avoided The weight of the baby was the only criterion for the drawing of conclusions because others (weeks of delivery toxemia frequency etc) involving greater technical errors than can occur when simply weighing in grams Analysis of the material for each year separately gave the same negative result concerning the effect of hospitalization on the weight of the baby in twin pregnancies

Because of the above finding it is now our policy also in the case of twin pregnancies to hospitalize only high risk patients

Apparently the regulatory mechanism triggering premature delivery (3) in twin pregnancies does not respond to bed rest This is not really very surprising because one major reason for premature delivery in twins is the stretch as stressed by one of the authors (M P) also in this Journal (8) Gravidas with twins who at admission for threatened premature labor had excessive peripheral plasma progesterone concentrations (221±12 ng/ml) in the 33rd week of pregnancy delivered mature (2 943±89 g) newborns whose total weight was 5 885±193 g in the 38th week of gestation In contrast to this gravidas with normal progesterone concentrations (163±9 ng/ml) delivered premature (2 254±75 g) twins who together weighed only *4 508±83 g in the 35th week of gestation* (2 3)

There is no reliable method for predicting the pre

Table I *Does bed rest influence the weight of the baby in twin pregnancies?*

	Number	Age	Mean ± SEM		
			Parity	g A	g B
Bed rest[1 2]	n = 116	27 0±0 4	0 7±0 1	2 658±40	2 634±47
No bed rest[2]	n = 119	28 0±0 5	1 0±0 1	2 631±43	2 570±46
Single births[3]	n = 35	26 0±0 3	0 7±0 1	3 419±37	—

1 = at least 14 days of hospitalization after 32nd week of pregnancy
= deliveries in pregnancy week 34 or later
3 = born after a twin

mature delivery of twins Efforts should therefore be made to define more precisely the stretch and proges teronegenesis

REFERENCES

1 Ahlström K Prematurprofylax vid tvillinggraviditet Läkartidningen *71* 3089 1974
2 Csapo A I & Pulkkinen M O Unpublished observation Cited by A I C *In* The fetus and birth Ciba Foundation Symp 47 (new series) p 187 Elsevier/Excerpta Medica Amsterdam 1977
3 Csapo A I & Pulkkinen M O Control of human parturition *In* Progress in Perinatology p 159 (ed Leslie Iffy and Harold Kaminetzky) Stickley Philadelphia 1977
Dawood M Y Ratnam S S & Lim Y C Twin pregnancy in Singapore Aust N Z J Obstet Gynaecol *15* 93 1975
Komaromy B & Lampe L The value of bed rest in twin pregnancies Int J Gynaecol Obstet *15* 262 1977
6 Mac Gillivray I *In* Human Multiple Reproduction (eds I Mac Gillivray P P S Nylander and G Corney) *Saunders London 1975*
7 Nilsson B A Värdering av en diagnostik metod Suom Lääk I *34* 1121 1979
8 Pulkkinen *M O & Kivikoski A Stretch* as a uterine stimulant Letter to the Editor Acta Obstet Gynecol Scand *52* 93 1973
9 Twin pregnancy Acta Obstet Gynecol Scand Suppl 44 1975
10 Weekes A R L Menzies D N & De Boer C H The relative efficacy of bed rest cervical suture and no treatment in the management of twin pregnancy Br J Obstet Gynaecol *84* 161 1977

Submitted for publication November 28 1979

M O Pulkkinen M D
Department of Obstetrics and Gynecology
University of Turku
SF 20520 Turku 52
Finland

ACTA OBSTETRICIA ET GYNECOLOGICA SCANDINAVICA

Volume 58, 1979

Published by
the Nordic Association for Obstetrics and Gynecology
Editor
Professor Ingemar Joelsson

Address
Box 443 S-901 09 Umeå Sweden

Distributed by Acta Obstetricia et Gynecologica Scandinavica
Box 443 S 901 09 Umeå Sweden

ISSN 0001-6349

Printing and binding by
Nyheternas Tryckeri AB Umeå Sweden 1979

AUTHORS INDEX

of volume 58 year 1979

arnoudse J G Complications of cerclage 255
badir A see Gal 429
bramovici H see Thaler 239
datto R see Miodovnik 565
dlercreutz H see Laatikainen 95
doni A see Miodovnik 565
gmon M see Goldman 415
lapiessa U Pharmacodynamic studies with a new progestational substance Org 2969 in combination with ethinyloestradiol suppl 85
llgén L G Biological fate of methenamine in man 287
msterdam E see Levin 371
nderman S see Jaschevatzky 175
ndersen A N Treatment of hyperprolactinemic luteal insufficiency with bromocriptine 379
Andersson K E see Ulmsten 115
Andersson K E Side-effects of prostaglandin synthetase inhibitors suppl 87 p 101
Andersson K E see Ulmsten 547
Andersson K E see Wingerup suppl 84 p 11
Andersson K E see Wingerup suppl 84 p 15
Aragon G see Lunell 443
Arffmann E see Johansen 265
Arocha Pinango C L Is there a physiological intravascular coagulation in obstetrical cases? 27
Aspegren K see Trope 543
Assendorp R see Alapiessa suppl 85
Backman C see Sandström suppl 88 p 49
Bakketeig L see Bergsjø 129
Barany S see Dandenell suppl 87 p 95
Batra S The regulation of oestradiol and progesterone concentrations in the female reproductive tissues suppl 82
Beazley J M Body weight in parous women Is there any alteration between successive pregnancies? 45
Ben Efraim S see Halbrecht 411
Bengtsson R see Magno 81
Benumof J L see Bryson 497
Berg A Å son see Weiner suppl 88 p 65
Bergan T see Onsrud 401
Bergqvist A Acute deep vein thrombosis (DVT) after cesarean section 473
Bergqvist D see Bergqvist A 473
Bergsjø P Socioeconomic implications of dysmenorrhea suppl 87 p 67
Bergsjø P Duration of labour with spontaneous onset 1 9
Bergström S Amniotic fluid cell exfoliation in early human pregnancy 353
Beyth Y see Sadovsky 313
Bieglmayer Ch see Spona suppl 88 p 7
Bille Brahe N E Red cell 2 3-diphosphoglycerate in pregnancy 19
Bompiani A see Cittadini 393
Brandes J M see Thaler 239
Bremme K see Lundström 231
Bremme K see Bygdeman suppl 87 p 33
Bremme K Prophylactic salpingo-oophorectomy in cancer of the cervix 183
Briel R C Platelet function coagulation and fibrinolysis during termination of missed abortion and missed labor by $PGF_{2\alpha}$ and oxytocin 361
Brohult A Effect of alkoxyglycerols on the frequency of fistulas following radiation therapy for carcinoma of the uterine cervix 203
Brohult J see Brohult A 203
Brohult S see Brohult A 203
Brook I see Levin 371
Bryson T K Uterine rupture caused by midtrimester saline abortion 497
Bukovsky I see Weinraub 217
Bunne G see Öbrink 91
Bunne G see Öbrink 123
Bygdeman M Effects of the prostaglandins on the uterus Prostaglandins and uterine contractility suppl 87 p 33
Bäckström T Plasma progesterone concentrations after administration via intravaginal rings 211
Bøggild Madsen N B see Møller 481
Canales E S see Guzmán 53
Carelli G see Cittadini 393
Carlström K see Lunell suppl 88 p 17
Carlström K Serum levels of total dehydroepiandrosterone and total estrone in postmenopausal women with special regard to carcinoma of the uterine corpus 179
Caspi E see Weinraub 217
Castaldo F see Cittadini 393
Cavalli Björkman K see Jacobson suppl 87 p 73
Chan W Y see Fuchs suppl 87 p 91
Choudry R see Gal 429
Cittadini A Water and ion metabolism in placenta II Water compartments and electrolytes in slices of rabbit placenta at different periods of gestation incubated at 0–1 C 393
Collen J see Öbrink 123
Cordesius E see Gustavii 409
Cova A see Arocha Pinango 27
Cullberg G Some adverse effects of copper IUD 87
Dahlström J A see Sandström suppl 88 p 49
Dalaker K Delayed reproductive complications after induced abortion 491
Damber M-G see Carlström 179
Damber M-G A new and sensitive method to quantify

and compare the biological potency of various estrogens in man 527
Dandenell L O Clinical experience of naproxen in the treatment of primary dysmenorrhea suppl 87 p 95
Date J see Rolschau 343
Dawood M Y see Fuchs suppl 87 p 91
De Gezelle H Puerperal lactation suppression and prolactin 469
De Grandi P Abscess formation of a Gartner s duct cyst with cervical communication in a case of bicornuate uterus associated with an ipsilateral renal agenesis 503
Delcourt A see Naeije 531
Dhont M see De Gezelle 469
Dollberg L see Miodovnik 565
Dottori O see Matouskova suppl 83 p 9
Drogendijk A C see Meir van 221
Düsterberg B Plasma levels of active ingredients after single and repeated administration of a new oral contraceptive containing 2 mg of cyproterone acetate and 50 µg of ethinyl estradiol (Diane[R]) to five young women suppl 88 p 27
Dutt T P see Gordon Wright 23
Ehrström Ch Fetal movement monitoring in normal and high risk pregnancy suppl 80
Eikhom S N see Bergsjø 123
Einhorn N see Bremme 183
Elder M G see Gordon Wright 23
Elmén H see Matouskova suppl 83 p 43
Eneroth P see Lundström 231
Erkkola R see Lamminтausta 447
Eskildsen P C see Andersen 379
Falck Larsen J see Hertz 365
Farina J R ee Bryson 497
Fattah M M A see Sammour 535
Fedor Freybergh P see Öbrink 91
Feingold M The peroxidase content and the antibacterial vity of the amniotic fluid 49
S External cephalic version in the management of presentation with special reference to placenta ion 209
S Minimal brain dysfunction in children born in *breech presentation 295*
Finnström O see Tylleskär 513
Fischer F L see Huggins 65
Forssman L see Matouskova suppl 83 p 9
Fredholm B B see Lunell 443
Fu Wang C Pregnancy following treatment with human gonadotropins in primary unexplained infertility 141
Fuchs F Suppression of menstrual prostaglandins and relief of dysmenorrhea with ibuprofen *suppl* 87 p 91
Fuchs T see Hammarström 417
Furuhjelm M Present status of estrogen treatment for prevention of postmenopausal osteoporosis suppl 88 p 97
Furuhjelm M see Carlström 179
Gal D Segmental epidural analgesia for labor and delivery 429
Gambrell R D The role of hormones in the etiology of breast and endometrial cancer suppl 88 p 73
Garcia C R see Huggins 65
Gemzell C see Fu Wang 141
Gennser G see Marsál 335
Gennser G see Marsál 197
Gennser G see Grennert 3
Gillespie A see Bygdeman suppl 87 p 33
Gjønnæss H see Onsrud 401
Goldman J A Arteriography and chemotherapy in localized trophoblastic disease by means of local (pelvic) intraarterial infusion 415
Gordon Wright A P The routine use of oral prostaglandin E_2 tablets for induction or augmentation of labor 23
Granström E Prostaglandin chemistry suppl 87 p 13
Green K Determination of prostaglandins in body fluids and tissues suppl 87 p 15
Green K see Lundström suppl 87 p 51
Grennert L On improved outcome of twin pregnancies 3
Grünstein S see Jaschevatzky 175
Grönroos M see *Punnonen* 101
Grönroos M see Pulkkinen 569
Grönroos M Treatment of vulval epithelial lesions by pulsed high frequency therapy 187
Grönroos M see Johansson 213
Grönroos M Pregnancy and delivery after conization of the cervix 477
Grönroos M see Liukko 275
Gupta I M see Gupta S 507
Gupta S In situ carcinoma of the uterine cervix showing superficial endometrial spread 507
Gustafson A see Sjöverstolpe suppl 88 p 89
Gustavii B Fetoscopy 409
Guzmán V Improvement of defective lactation by using oral metoclopramide 53
Hajj S see Karam 73
Halbrecht I Mixed wife husband leukocyte migration inhibition test after normal pregnancy 411
Hallböök T see Bergqvist 473
Haller W S see Varma 439
Hammarström L The immunodepressive effect of human *glucoproteins and their possible role in the nonrejection* process during pregnancy 417
Hansen J T see Møller 481
Hansen R see Nielsen 495
Hanson B see Matouskova suppl 83 p *15*
Hanson B see *Matouskova* s ppl 83 p 31
Hanson B see *Matouskova suppl* 83 p 43
Hanssen K F see Kulseng Hanssen 245
Hasch E Prediction of the time of delivery by means of *ultrasonic scanning between the 20th and 30th weeks of* pregnancy 457
Hashiba N see Nakano 59
Hedenskog S see Tylleskär 513
Heine M W see Varma 439
Helmius G see Weiner *suppl* 88 p 65
Henriksen H M The cryosurgical treatment of intra epithelial neoplasia 271
Henzl M R Naproxen and naproxen sodium in dysmenorrhea Development from *in vitro* inhibition of prostaglandin synthesis to suppression of uterine contractions in women and demonstration of clinical efficacy suppl 87 p 105
Hertz J B Estradiol estriol and human placental lactogen in serum in threatened abortion 365
Hirvonen E see Alapiessa suppl 85

Hjelmkvist M see Öbrink 91
Hollmen A see Jouppila 249
Hollmen A see Jouppila 135
Holmberg G see Allgén 287
Homma, A see Nielsen 309
Honore L H Menorrhagia diffuse myometrial hyper trophy and the intrauterine contraceptive device 283
Hook E B see Little 15
Hümpel M see Düsterberg suppl 88 p 27
Huggins G R Emotional distress in morning after pill patients 65
Huisjes H J see Aarnoudse 255
Hulkko S see Alapiessa suppl 85
Ibrahim F K see Sammour 535
Ikonen S see Lau lahti 163
Ingerslev M Failure of fusion between an upper and a lower segment of the vagina 215
Insler V see Feingold 49
Insler V see Levin 371
Ishiguro T Neutralizing antibodies against herpes simplex virus in maternal and umbilical cord serum 413
Izu A see Henzl suppl 87 p 105
Izu A see Sande suppl 87 p 93
Jacobson J Prostaglandin synthetase inhibitors and dys menorrhea A survey and personal clinical experience suppl 87 p 73
Janbu T Effect of acetylsalicylic acid paracetamol and placebo on pain and blood loss in dysmenorrheic women suppl 87 p 81
Janecek P see De Grandi 503
Jaschevatzky O E The treatment of postmenopausal syndrome by monthly oral doses of Quinestrol 175
Jenssen H Fetal systolic time intervals in late pregnancy effect of atropine 519
Jenssen H see Nesheim 41
Joelsson I see Carlström 179
Joelsson I The effect of inhibitors of prostaglandin synthesis in primary dysmenorrhea studied with hystero-metry suppl 87 p 45
Joelsson I Determination of tonicity in the nonpregnant human uterus in vivo 555
Joelsson I see Fianu 295
Joelsson I see Brohult 203
Johansen P Evaluation of smears obtained by cervical scraping and an endocervical swab in the diagnosis of neoplastic disease of the uterine cervix 265
Johansson E D B see Weiner suppl 88 p 23
Johansson I see Weiner suppl 88 p 65
Johansson R Oestrogen receptors in dysplastic and malignant vulval tissue 213
Johnsen S G see Hertz 365
Johnsson J E Recurrences and metastases in carcinoma of the uterine body correlated to the size and localiza tion of the primary tumor 405
Jouppila P Effect of induction of general anesthesia for cesarean section on intervillous blood flow 249
Jouppila P see Jouppila R 135
Joppuila P Vaginal bleeding in the last two trimesters of pregnancy A clinical and ultrasonic study 461
Jouppila R see Jouppila P 249
Jouppila R Segmental epidural analgesia in labour Related to the progress of labour fetal malposition and instrumental delivery 135
Järvi K see Alapiessa suppl 85
Järvinen P A see Ylöstalo 279
Kajanoja P Naproxen and indomethacin in the treatment of primary dysmenorrhea suppl 87 p 87
Kampf D see Jaschevatzky 175
Karam K Hyperthecosis syndrome 73
Karinen J M see Jouppila 135
Karjalainen O see Mandelin 169
Kauppila A see Ylikorkala 453
Kauppila E see Ylöstalo 279
Kidess E see Briel 361
Kilkku P see Liukko 275
Kilkku P see Grönroos 477
Kirschner R Pregnancy in a non-communicating rudimentary uterine horn A reason for failed therapeutic second trimester abortion 499
Kirstein Pedersen A see Ulmsten suppl 84 p 19
Kjeldsen J Hemodynamic investigations during labour and delivery suppl 89
Knoth M see Andersen 379
Koller O Fetal growth retardation associated with inadequate haemodilution in otherwise uncomplicated pregnancy 9
Komlos L see Halbrecht 411
Korhonen M see Alapiessa suppl 85
Kouvonen I see Punnonen 389
Kuovonen I see Johansson 213
Kristoffersen E see Nielsen 309
Kristoffersen K see Rolschau 343
Kuikka J see Jouppila 249
Kullander S see Grennert 3
Kullander S see Trope 543
Kullander S Bromocriptine treatment of the premenstrual syndrome 375
Kulseng Hanssen S Serum prolactin and thyroid stimulating hormone levels following thyreotropin releasing hormone stimulation in preeclamptic patients 245
Kunz S see Briel 361
Kurjak A Ultrasound diagnosis of fetal abnormalities in multiple pregnancy 153
Kuusi T see Tikkanen suppl 88 p 83
Käär K see Alapiessa suppl 85
Laatikainen T Plasma medroxyprogesterone acetate levels following intramuscular or oral administration in patients with endometrial adenocarcinoma 95
La hnit Fixson U The development and evaluation of an ovulation inhibitor (Diane[R]) containing an antiandrogen suppl 88 p 33
Lalos O see Joelsson suppl 87 p 45
Lalos O see Joelsson 555
Lalos O see Dandenell suppl 87 p 95
Lambercy J M see De Grandi 503
Lammintausta R Effect of long term salbutamol treatment on renin aldosterone system in twin pregnancy 447
Lange A P see Hasch 457
Langer R see Weinraub 217
Larsen J F see Andersen 379
Larsen T see Nielsen 495
Larsson B see Cullberg 87
Larsson-Cohn U Effects of three different combinations

of ethinyl estradiol and levonorgestrel on plasma lipids and high density lipoproteins suppl 88 p 57
Latin V see Kurjak 153
Laudanski T Hormonal factors in the regulation of myometrial activity An in vivo study suppl 91
Lauersen N H Investigation of prostaglandins for abortion suppl 81
Laufer N see Sadovsky 313
Lauslahti K Placenta as an indicator of fetal postnatal prognosis 163
Lauslahti K see Alapiessa suppl 85
Lebech P E see Ottesen 423
Leeuwen van M see Wolfs suppl 90
Lehtovirta P see Paavonen 301
Leijon I see Tylleskär 513
Levin S see Feingold 49
Levin S The effect of missed abortion and spontaneous abortion on the fate of subsequent pregnancies 371
Lichtenberg S M see Dalaker 491
Linares J see Arocha Pinango 27
Lindbæk E see Nesheim 41
Lindberg B S Maternal sepsis uterine rupture and coagulopathy complicating cervical cerclage 317
Lindström K see Ulmsten 547
Lisciak J see Dandenell suppl 87 p 95
Little R E Maternal alcohol and tobacco consumption and their association with nausea and vomiting during pregnancy 15
Liukko P see Grönroos 187
Liukko P see Grönroos 477
Liukko P Methods for evaluating the intrauterine location of carcinoma 275
Liukko P see Alapiessa suppl 85
Lumiala I see Alapiessa suppl 85
Lundström V Serum beta human chorionic gonado
levels in the early diagnosis of ectopic pregnancy
V see Bygdeman suppl 87 p 33
V see Jacobson suppl 87 p 73
V Endogenous prostaglandins in dys
the effect of prostaglandin synthetase inhibitors (PGSI) on uterine contractility suppl 87 p 51
Lunell N O Circulatory and metabolic effects of acute $beta_1$ blockade in severe pre-eclampsia 443
Lunell N-O *Ovulation inhibition with a combined oral* contraceptive containing 20 μg ethinyl estradiol and 250 μg levonoregestrel suppl 88 p 17
Lunell N-O see Carlström 179
Lykkesfeldt G A comparison of three methods for inducing labor Oral prostaglandin E_2 buccal desamino-oxytocin intravenous oxytocin 321
Löfberg L see Gustavii 409
Löfgren O see Marsál 335
Löfgren O see Marsál 197
Löfstrand T see Kirschner 499
Løkken P see Janbu suppl 87 p 81
Lövgren T see Punnonen 389
Lövgren T see Johansson 213
Magno R Acid base balance during laparoscopy 81
Maltau J M Effects of betamethasone on plasma levels of estriol cortisol and HCS in late pregnancy 235
Mandelin M Menstrual regulation as a method for early termination of pregnancy 169
Marboe C C see Naeye 37
Mark J see Kirschner 499
Marsål K Fetal breathing movements and maternal exercise 197
Marsål K Effects on fetal breathing movements of maternal challenges Cross over study on dynamic work static work passive movements hyperventilation and hyperoxygenation 335
Martinez P see Arocha Pinango 27
Matouskova A Epidural analagesia Continuous mini infusion of bupivacaine into the epidural space during labour suppl 83
Matouskova A An improved method of epidural *analgesia with reduced instrumental* delivery rate suppl 83 p 9
Matouskova A Continuous mini infusion of bupivacaine into the epidural space during labor Part I Radiographic visualization of the epidural catheters suppl 83 p 15
Matouskova A Continuous mini infusion of bupivacaine into the epidural space during labor Part II Blood concentration of bupivacaine suppl *83 p 31*
Matouskova A Continuous mini infusion of bupivacaine into the epidural space during labor Part III A clinical study of 225 parturients suppl 83 p 43
Medegård A see Magno 81
Meir van J M Colposcopy in a case of suspected genital herpes infection in early pregnancy 221
Meirik O Demographic techniques in describing contraceptive use applied on the situation in Sweden suppl 88 p 61
Melsen van A see Naeije 531
Micic S see Andersen 379
Miodovnik M Vulvar eosinophilic granuloma 565
Moe N see Maltau 235
Mommsen S see Møller 481
Møller B R *Effect of althesin anesthesia* on blood loss during therapeutic abortion A comparison with local and thiopental anesthesia 481
Naeije R Enhancement of the amylase-creatinine ratio in pregnancy 531
Naeye R L Perinatal death due to abruptio placentae in an African city 37
Nakano R Diagnostic evaluation of progesterone 59
Nesheim B I Neurobehavioral response *of infants after* paracervical block during labour 41
Nesheim B I see Janbu suppl 87 p 81
Neuray F see Naeije 531
Newton J R see Reading 105
Nielsen J see Andersen 379
Nielsen J X/X translocation and Turner s syndrome in a women with climacterium praecox 309
Nielsen N C Heat induction in copper bearing *IUD s* during short wave diathermy 495
Nieminen U see Laatikainen 95
Nikkilä E A see Tikkanen suppl 88 p 83
Nillius S J see Weiner suppl 88 p 23
Nillius S J see Wiqvist suppl 87
Nilsson B see Dandenell suppl 87 p 95
Nilsson B see Wiqvist suppl 87
Nilsson B see Jacobson suppl 87 p 73
Norbeck M see Jacobson suppl 87 p 73

Nygren K G see Meirik suppl 88 p 61
Nygård I see Lundström 231
Nyholm H Serum testosterone FSH/LH and urinary excretion of estrogens and corticoids during treatment with an injectable longacting estrogen DHEA preparation 385
O Herlihy C Early successful pregnancy following tuberculous endometritis 57
Obel E Pregnancy complications following legally induced abortion with special reference to abortion technique 147
Obel E see Weber 259
Obel E Fertility following legally induced abortion 539
Obel E B see Weber 347
Obel E B Pregnancy complications following legally induced abortion 485
Olcott A see Møller 481
Ollanketo M L see Ylikorkala 453
Onsrud M Amoxycillin absorption and penetration in pelvic inflammatory disease 401
Osler M Standard treatment of dysmenorrhea with special reference to treatment with spasmolytics and hormones suppl 87 p 69
Osler M see Lykkesfeldt 321
Ottesen B Plasma progesterone serum estriol and plasma HPL determinations during the last trimester to detect changes before spontaneous labor 423
Ozaki Y see Ishiguro 413
Paavonen J A Infertility and cervical chlamydia trachomatis infection 301
Pallesen G see Johansen 265
Palti Z see Miodovnik 565
Paparella P see Cittadini 393
Parewyck W see De Gezelle 469
Patek E Quinacrine hydrochloride 561
Paterson M E L The aetiology and outcome of abruptio placentae 31
Peleg D see Goldman 415
Persson B see Allgén 287
Persson B see Lunell 443
Persson P H see Ulmsten 547
Persson P H see Grennert 3
Philipson A Plasma and urine levels produced by an oral dose of ampicillin 0 5 g administered to women taking oral contraceptives 69
Pickles V R Prostaglandins and dysmenorrhea Historical survey suppl 87 p 7
Pirker R see Spona suppl 88 p 7
Plesner R see Nyholm 385
Pora O see Alapiessa suppl 85
Pulkkinen M O Bed rest did not prevent prematurity in twins because the etiology lies in the stretch and poor progesteronegenesis 569
Pulkkinen M O Suppression of uterine activity by prostaglandin synthetase inhibitors suppl 87 p 39
Punnoner R see Grönroos 187
Punnonen R Uterine and ovarian estrogen receptor levels in climacteric women 389
Punnonen R see Grönroos 477
Punnonen R see Liukko 275
Punnonen R Squamos cell carcinoma in situ from the uterine cervix to the distal end of the fallopian tube 101
Punnonen R see Alapiessa suppl 85
Railsback K see Varma 439
Ramadan M A see Sammour 535
Rantakylä P see Ylöstalo 279
Rauramo L see Grönroos 187
Rauramo L see Punnonen 389
Reading A E A card sort method for pain assessment in gynaecology A multidimensional approach 105
Reed C see Reading 105
Rhen K see Alapiessa suppl 85
Rickels K see Huggins 65
Rolschau J Folic acid supplement and intrauterine growth 343
Romor R see Cittadini 393
Romslo I see Sagen 305
Rosenfeld D L see Huggins 65
Row A D see Varma 439
Rubinstein E Initiating events and promoting agents in cervical neoplasia viral epithelial lesions 509
Ruokonen A see Alapiessa suppl 85
Rydén G see Tylleskär 513
Rørth M see Bille Brahe 19
Rösmark U see Matouskova suppl 83 p 15
Sadovsky E The role of fetal movements assessment in cases of severe Rh immunized patients 313
Sagen N see Koller 9
Sagen N Plasma estriol progesterone cortisol placental lactogen and alpha fetoprotein in a pregnancy with an anencephalic fetus followed from the seventh week till term 305
Saikku P see Paavonen 301
Salmi T Risk factors in endometrial carcinoma with special reference to the use of estrogens suppl 86
Salvesen T see Sande suppl 87 p 93
Sammour M B Nucleic acids and protein changes in normal and pre-eclamptic placentae 535
Samsio G see Silfverstolpe suppl 88 p 89
Sande H A Treating dysmenorrhea with anti inflammatory agents A double blind trial with naproxen sodium suppl 87 p 93
Sandström B see Dandenell suppl 87 p 95
Sandström B see Damber 527
Sandström B Adjustments of circulation including blood pressure to orthostatic reaction and physical exercise during application of a low estrogen dose steroid oral contraceptive suppl 88 p 49
Saranen M see Alapiessa suppl 85
Schneider D see Weinraub 217
Schneider W H F see Spona suppl 88 p 7
Schoultz B von see Carlström 179
Schoultz B von see Damber 527
Schoultz B von see Bäckström 211
Schroeder R see Spona suppl 88 p 7
Serup J Vaginal fine needle and large needle aspiration biopsy in large pelvic tumors indicating advanced ovarian carcinoma A new technique 125
Shalit A see Jaschevatzky 175
Shapiro G see Goldman 415
Silfverstople G Lipid metabolic studies in oophorectomized women Effects of three different progestogens suppl 88 p 89
Sjöberg N-O Dysmenorrhea and uterine neurotransmitters suppl 87 p 57

Skjaeraasen J Amniotic fluid phosphatidylinositol and phosphatidylglycerol I Normal pregnancies 225

Skjaeraasen J Amniotic fluid phosphatidylinositol and phosphatidylglycerol II Diabetic and preeclamptic pregnancies 433

Skjaeraasen J Amniotic fluid phospholipid concentrations in pregnancy with pre-eclampsia and/or intrauterine growth retardation of the fetus 191

imedby B see Meirik suppl 88 p 61

imith C I E see Hammarström 417

ipona J Ovulation inhibition with different doses of levonorgesetrel and other progestogens Clinical and experimental investigations suppl 88 p 7

itenberg P see Ulmsten suppl 84 p 19

itigbrand T see Damber 527

itokke K T see Maltau 235

itorm Mathisen I see Nesheim 41

itray Pedersen S see Skjaeraasen 225

itray Pedersen S see Skjaeraasen 433

iströmberg P see Gustavii 409

itøa K F see Sagen 305

Sundvall M see Lundström 231

Svanberg L see Kullander 375

Svanborg A see Silfverstolpe suppl 88 p 89

Svanborg K see Lundström suppl 87 p 51

Svenstrup B see Hertz 365

Svenstrup B see Andersen 379

Swinhoe J R see Beazley 45

Sörbo B see Allgen 287

Sørensen T see Hasch 457

Tafari N see Naeye 37

Tancer M L see Gal 429

Tarkkila T see Alapiessa suppl 85

Terranova T see Cittadini 393

Thaler I Serum and amniotic fluid heat labile alkaline iosphatase and amniotransferases in association with im stained liquor 239

M see De Gezelle 469

G Regional changes in structure and function of iergic nerves in guinea pig uterus during pregnancy uppl 79

Tikkanen M J Treatment of post menopausal hypercholesterolaemia with estradiol suppl 88 p 83

Tiwari P V see Gupta S 507

Tjernberg B see Öbrink 123

Toivonen J see Bäckström 211

Tojo S see Nakano 59

Torjesen P A see Kulseng Hanssen 245

Toscano G see Guzmán 53

Tronstad S E see Magno 81

Trope C Heterogeneous response of disseminated human ovarian cancer to cytostatics in vitro 543

Tylleskär J Spontaneous labor and elective induction A prospective study 513

Ulmsten U Multichannel intrauterine pressure recording by means of microtransducers 115

Ulmsten U Determination of myometrial tension during labor by combined microtransducer IUP recording and ultrasonic examination of the uterine cavity 547

Ulmsten U Cervical ripening induced by prostaglandin E in viscous gel suppl 84

Ulmsten U Aspects of the ripening of the cervix and induction of labor by intracervical application of PGE_2 in viscous gel suppl 84 p 5

Ulmsten U see Wingerup suppl 84 p 11

Ulmsten U see Wingerup suppl 84 p 15

Ulmsten U A new gel for intracervical application of prostaglandin E suppl 84 p 19

Ulstein M see Koller 9

Ulstein M see Sagen 305

Ung K A see Gal 429

Vaajalahti P see Punnonen 101

Vaclavincová V see Fianu 209

Varma K Ratio of amniotic fluid cortisol and maternal serum cortisol (AFC/MSC) as an index of fetal lung maturity 439

Varma S K see Varma K 439

Vartiainen E see Tikkanen suppl 88 p 83

Vaula D see Koller 9

Vesanto T see Kajanoja suppl 87 p 87

Vesterinen E see Paavonen 301

Vestergaard Andersen T B see Møller 481

Victorin L see Matouskova suppl 83 p 9

Viinikka L see Alapiessa suppl 85

Virkkunen P see Alapiessa suppl 85

Vugt van P J H The protrusions from the cervical cana at the scar of a previous cesarean section 327

Wallentin L see Larsson Cohn suppl 88 p 57

Washio M see Nakano 59

Weber T Pregnancy complications following conizatioi of the uterine cervix (I) 259

Weber T Pregnancy complications following conizatioi of the uterine cervix (II) 347

Weijers M see Alapiessa suppl 85

Weiner E Pituitary responsiveness to luteinizing hormone releasing during treatment with subdermal D norgestrel implants in women suppl 88 p 23

Weiner E Contraception for teenage girls Combination pill or IUD? suppl 88 p 65

Weinraub Z Ultrasonographic diagnosis of fetal ascites in a twin pregnancy 217

Wendt H see Düsterberg suppl 88 p 27

Whittle B J R Prostaglandin synthetase inhibitors Drugs which affect arachidonic acid metabolism suppl 87 p 21

Wide L see Weiner suppl 88 p 23

Widholm O see Wiqvist suppl 87

Widholm O Dysmenorrhea during adolescence suppl 87 p 61

Widholm O see Alapiessa suppl 85

Wielenga G see Meir van 221

Wingerup L see Ulmsten suppl 84

Wingerup L Ripening of the cervix and induction of labor in patients at term by single intracervical application of prostaglandin E_2 in viscous gel suppl 84 p 11

Wingerup L Ripening of the cervix by intracervical application of PGE_2 gel before termination of pregnancy with dilatation and evacuation suppl 84 p 15

Wingerup L see Ulmsten suppl 84 p 19

Wiqvist N Dysmenorrhea and prostaglandins Proceedings of an international symposium in Helsinki November 16-17 1978 suppl 87

Wiqvist N Dysmenorrhea and prostaglandins suppl 87 p 5

Wladimiroff J W see Meir van 221
Wolfs G M J A Electromyographic observations on the human uterus during labour suppl 90
Ylikorkala O Intramuscular ACTH or placebo in the treatment of hyperemesis gravidarum 453
Ylöstalo P Intrauterine progesterone contraceptive system as an alternative in cases where conventional IUD s are unsuitable 279
Zador G see Furuhjelm suppl 88 p 97
Zador G see Sandström suppl 88 p 49
Zador G Fertility regulation using triphasic administration of ethinyl estradiol and levonorgestrel in comparison with the 30 plus 150 μg fixed dose regime suppl 88 p 43
Zador G New leads on hormonal contraception and hormone therapy of the climacteric and menopause suppl 88
Zador G see Lunell suppl 88 p 17
Zador G see Larsson Cohn suppl 88 p 57
Zárate A see Guzmán 53
Zinder O see Thaler 239
Åkerlund M Pathophysiology of dysmenorrhea suppl 87 p 27
Åstedt B see Tropé 543
Åström H see Lunell 443
Öbrink A Mental factors influencing recurrence of stress incontinence 91
Öbrink A Estrogen regimen in women with endometrial carcinoma at Radiumhemmet 1974-77 123
Økland G see Dalaker 491
Ölund A The effect of indomethacin on the instillation abortion interval in rivanol induced mid-trimester abortion 121